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The following questions were derived from those asked by medical directors on the management of postherpetic neuralgia in their elderly, long-term care residents.

1. Does age influence who will be left with postherpetic neuralgia (PHN) after shingles?

For the approximately 20% of the U.S. population who develop shingles,[1] age is the single most important predictor of who will be left with PHN.[2,3] The risk of PHN after childhood zoster is near zero,[4] and risk of PHN increases with age throughout the entire lifespan. Of course, given that age is also the major risk for contracting shingles in the first place,[5] it is quickly apparent that, with the exception of small specific groups of younger patients (eg, those with hematogenous malignancies or HIV), PHN is almost exclusively a disease of older patients. Zoster patients 50 years or older have a 27-fold higher prevalence of persistent **pain** 60 days after rash onset when compared to those under 50 years of age.[6] Because of the impact of age as a risk factor, clinicians who care for older adults need to be especially knowledgeable about zoster and how best to prevent and treat PHN.

2. What can I do for my patients with shingles to lessen the risk of PHN?

The actions of both patients and clinicians can markedly lessen the risk of PHN after shingles.[7,8] Patients need to be educated to seek immediate medical help for a shingles rash (or shingles-like **pain** even without rash). Similarly, physicians need to educate their office staff that patients phoning with shingles symptoms need to be seen that day, not next week. Probably because of its visible rash, shingles is often dismissed as trivial illness; in reality, shingles is most like a stroke because it involves the sudden death of irreplaceable neurons. Not surprisingly, recent data suggest that the risk of PHN is tightly coupled to the severity of

neuronal loss.9 This presumably underlies the protective effect of antiviral medications against PHN as well as symptoms of acute zoster including lesion healing and viral shedding.7

In the United States, three antiviral medications are commercially available for oral administration to treat zoster: acyclovir,10 famciclovir,11 and valacyclovir.12 While famciclovir (500 mg) and valacyclovir (1 g) are taken three times daily, they are more expensive than acyclovir (800 mg), which needs five daily doses; all should be taken until no new lesions appear, for at least 7 days. All antiviral medications are analogues of viral nucleotides and have only minimal interactions with mammalian cells. Clinical trials and experience have shown that these medications are extremely well tolerated, with no significant side effects. Isolated cases of nephrotoxicity have been associated with high-dose parenteral acyclovir, but not with the regimen used for zoster.13 The risk-benefit ratio for antivirals is so favorable that they should be administered in virtually all known cases of zoster and used even when there is just a suspicion of zoster, especially in older patients. This is because unilateral **pain** and sensory symptoms limited to a single dermatome without rash can represent the first signs of zoster (preherpetic neuralgia) or zoster without visible rash (sine herpete). Preherpetic neuralgia is experienced by 75% of shingles patients and has been shown to be an independant risk factor for PHN after shingles.11 Thus, antivirals should be given even in the absence of a rash if there is a suspicion of zoster.

3. Should tricyclics be started during an episode of zoster to decrease the risk of PHN?

One important study found that low doses of tricyclic antidepressants (TCAs) (amitriptyline, 25 mg daily) given for 90 days within the first months after zoster onset can halve the risk of PHN, independent of use of antivirals.8 Thus, amitriptyline may be a second disease-modifying treatment. However, the U.S. General Accounting Office has termed the use of amitriptyline in patients over 65 "inappropriate" because of the drug's many side effects, particularly in geriatric patients.14 The American Geriatrics Society's Panel on Chronic **Pain** in Older Persons concurs.15 Fortunately, a randomized controlled trial documented equal efficacy of nortriptyline and amitriptyline for treatment of PHN and confirmed the superior side-effect profile of nortriptyline.16 In light of these data, I prescribe nortriptyline rather than amitriptyline for neuroprotection in shingles patients with **pain** and urge patients to continue taking it, even if only low doses are tolerated, for at least 90 days or until **pain** disappears.

4. What are the criteria for making a diagnosis of PHN?

PHN is loosely defined as persistent **pain** of any kind in and near the area of a healed shingles rash, but a more precise delineation between **pain** from acute shingles and PHN is needed to be able to correlate the results of research studies and develop guidelines applicable to individual patients. Although various timepoints have been used by various investigators, 3 months post-zoster is gaining acceptance as the most appropriate one. While some investigators measure time since the onset of rash resolution, this is a gradual event that cannot be assigned to one particular day. In contrast, almost all PHN patients remember (even years later) the day that their shingles rash began, much as one remembers the day of any major acute medical event. This date is usually documented in medical records as well. So, for these practical reasons, I recommend using 3 months following rash eruption to define the onset of PHN.

Of course, the transition from zoster **pain**, which is caused by combined acute tissue injury, neural inflammation, and **neuropathic pain**, to PHN, which in most patients does not reflect ongoing injury and inflammation,17 occurs gradually during the first year.18 It takes several weeks to a month for cutaneous integrity to be re-established, and longer for the intense inflammation of scar formation to resolve. The lesions of shingles are often full-thickness, with necrosis extending to the subcutaneous connective tissues. They are comparable to third-degree burns. With the most severe eruptions, patients may need hospital admission for advanced **pain** management including administration of intravenous or epidural opioids, or treatment such as skin grafting or plastic surgery. These can be particularly important for eruptions on the face. At a practical level, one can reassure patients that, for most people, **pain** resolves within 6 months of shingles onset.

5. Is it possible to diagnose PHN without witnessing the rash firsthand?

In many cases, the clinician asked to treat PHN did not witness the zoster that caused it. However, zoster is usually recognized by patient and physician alike, and most (but not all) patients will be left with permanent scars to confirm the diagnosis. Sometimes, one must look closely if there were only a few lesions, and some patients experience zoster sine herpete, with no known eruptions.19 These patients pose a diagnostic challenge. A careful sensory exam of the painful area using a pin to detect areas of reduced or abnormal sensation can confirm the neuralgic nature of the **pain** and localize the involved dermatome. If there are no sensory abnormalities, other sources of unilateral **pain**, such as musculoskeletal **pain** or **pain** referred from internal organs (especially the myocardium), should be considered. Musculoskeletal **pain differs** from neuralgic **pain** in that it usually worsens with activity and improves with rest and nonsteroidal anti-inflammatory treatments. In contrast, neuralgic **pain** is often improved by activity, when the patient's attention is focused elsewhere, and classically "worsens" when the patient is in bed at night with nothing else to think about.

There is only one other major cause of unilateral radicular torso **pain**, namely, nerve or root compression or irritation by a structural lesion. For this reason, I recommend imaging of the spine (and ribs) in such patients with no clear history or stigmata of prior shingles. This will detect the rare thoracic herniated discs, spinal meningiomas, schwannomas, and metastatic tumors that can cause radicular **pain** that mimics PHN. If imaging does not reveal a lesion, I treat that patient (particularly if they are middle-aged or older) for presumed zoster sine herpete with PHN. One can reassure such patients that the same medications are effective for all neuralgias regardless of etiology. Imaging is even more important for patients with trigeminal neuralgias of unclear etiology.

6. What are the best treatment options for established PHN?

Successful treatment of PHN will virtually always require the use of medications. As always, clinicians should rely on treatments for which there is published evidence of safety and efficacy. Randomized controlled trials are especially important because the natural history of shingles **pain** is to improve, particularly at first, so almost any treatment given soon after shingles will help many patients. Because of its frequency, well-defined date of onset and location, and single etiology, PHN is one of the most commonly used diseases to test new treatments for **neuropathic pain**, so there are ample well-designed trials to provide guidance. Most of the treatments proven efficacious will provide significant relief (with no or tolerable side effects) for half to two-thirds of PHN patients, leaving a substantial minority with **pain** resistant to treatment.

At present, results of randomized controlled trials support the use of four categories of medications to treat PHN (and other causes of **neuropathic pain**): noradrenergically active tricyclics, agents that suppress excess neuronal firing (often originally developed as anticonvulsants), opioids, and topical local anesthetics. Clinicians are urged to try at least one medication from each of these classes (if not contraindicated) before considering unproven therapies. Patients should be told that several medications might need to be tried. Emphasize that if clinician and patient work together, most patients will achieve substantial relief. Before initiating therapy, the specific **pain** symptoms that the patient experiences (eg, deep aching, surface **pain** from light touch, sudden lancinating pains) should be identified since individual symptoms may respond differentially. The initial medication should be the one most likely to be effective, and the dose increased steadily to either the maximally tolerated or target doses (see Table). Only if the primary analgesic is ineffective at the maximally tolerated dose should it be replaced with a second-line agent.

7. What is the role of antidepressants in treating PHN?

Although TCAs were originally FDA-approved for treating depression, they have largely been supplanted for that indication and are now often used off-label for treating **neuropathic pain**. Many well-designed trials have also established that their **pain**-relieving effects are independent of their antidepressant effects.20,21 Potentiation of descending inhibitory noradrenergic pathways appears to be critical for efficacy against **neuropathic pain**, because

antidepressants that only increase central nervous system (CNS) serotonin are ineffective for neuralgias.22,23

In younger patients, or unless medically contraindicated, tricyclics are a first treatment option because of long experience with their use, low cost, and potential disease-modifying effects.8 Although amitriptyline was the earliest TCA studied,20,24 and is still widely prescribed, it should be replaced (particularly in geriatric medicine) by desipramine21 and nortriptyline,16 which have fewer side effects. Nortriptyline, which can be sedating and thus is administered in the evening, is preferred for those with difficulty sleeping, whereas desipramine, which can be alerting and is usually given in the morning, can help patients who have daytime somnolence. (See Table for dosing and administration details.) Because of their long half-life, the dose should be increased no more often than once or twice weekly. Although some find relief with low doses, some may require and tolerate doses between 150-250 mg daily. Blood levels usually need not be monitored. These medications can take up to 6-8 weeks to achieve maximum benefit,21 so patients need to be advised to continue them for that period of time, despite the lack of apparent effect of a single dose. TCAs should be used with caution in patients with significant cardiovascular disturbances, which limits their use in geriatric patients.

8. What is the role of medications originally developed to treat epilepsy?

Neuropathic pain is caused by inappropriate and excess firing of **pain**-processing neurons, so it is logical that treatments originally developed to dampen uncontrolled neuronal activity in epilepsy should also be effective for **neuropathic pain**.25 This link has been so tight that new anticonvulsants under development are routinely evaluated against **pain** as well. Among older antiepileptic drugs, carbamazepine, FDA-approved for use in trigeminal neuralgia, has been found effective for PHN in one study.26 It is a useful secondary option when lancinating **pain** is a major symptom of PHN. I recommend use of the newer longer-acting formulations that need be taken twice daily (extended-release carbamazepine). Use of carbamazepine is limited by the need to monitor for the rare but serious adverse events of bone-marrow suppression27 and hepatotoxicity28 (see Table).

Among antiepileptics, gabapentin, a calcium-channel blocker,29 is the only first-line option for treating **neuropathic pain**; it has been tested in several controlled multicenter trials and has a recent FDA indication specifically for use in PHN.30-32 Gabapentin's utility derives not from greater efficacy but primarily from a lack of serious adverse effects and drug-drug interactions, and fewer minor adverse effects. This makes it an attractive initial treatment option for geriatric patients and for anyone at risk for side effects from tricyclics.

Higher doses (eg, 600-900 mg TID) are often needed to control **neuropathic pain** than those originally recommended for treatment of epilepsy. Because its half-life is about 6 hours, the number of pills can be increased rapidly, and maximum doses and benefit obtained within a few weeks. Yet, many PHN patients referred to **pain** management centers are on such low doses of gabapentin (eg, 100 or 300 mg TID) that it is impossible to know if it is helping. The obvious next step is to increase toward a full target dose, or until adverse effects develop. As with any other treatment, it is important not to leave patients on low doses of medications that are not clearly effective.

Doses can be increased as tolerated without the need to check blood levels. Most side effects are minor, occur during treatment initiation, and resolve within 10 days. Although gabapentin shares the common side effect of sedation, this occurs in fewer patients (20%) than for tricyclics.32 Dizziness and/or ataxia can occur, but less than for the tricyclics.31,32 Because of the risk of falls to the elderly, dizziness/ataxia, and orthostatic hypotension (occurs with TCAs but not with gabapentin) are potentially severe adverse effects. Peripheral edema is the most common specific side effect of gabapentin, occurring in about 5% of patients.32 Since gabapentin is metabolized entirely by the kidneys, dose reduction is recommended for patients with creatinine clearance of less than 60 mL/min. Absorption from the gut occurs via saturable transmucosal transporters, so if doses higher than 2700 mg daily are required, adding a fourth dose daily is more likely to be effective than simply increasing the amount taken at each of the three doses.

9. Is there a role for opioid medications in managing PHN?

Although it was earlier thought that opioid (morphine-like) medications were ineffective against **neuropathic pain**, this has been disproven in several well-designed clinical trials. Oral medications shown efficacious for PHN include oxycodone,33,34 morphine,35,36 tramadol,37 and methadone.36 Controlled-release oxycodone has been particularly well studied; one study documented that 25 of 90 otherwise intractable PHN patients reported good or excellent relief, with 50 others reporting mild to moderate relief.34

Despite concerns, cognitive side effects appear to be no more a problem than for other treatments. One recent randomized double-blind, placebo-controlled, crossover trial that compared opioids (morphine or methadone) head-to-head against TCAs for the treatment of PHN documented that while both provided effective **pain** relief (although not always for the same patients), more patients preferred opioids (54%) to TCAs (30%).36 Adverse cognitive effects occurred in the TCA-treated group, but no change in tests of cognitive function occurred in the opioid-treated group.36

Addiction is another theoretical concern that has not been a major problem among actual PHN patients. Several factors make PHN patients less likely to use opioid medications inappropriately, including advanced age, preponderance of women (among geriatric patients), and the fact that scarring from shingles provides objective evidence of disease.38 Patients should always be asked about any prior or current history of substance abuse; a positive response should provide a strong contraindication to the use of opioids, but experience treating cancer patients has established the low risk of the onset of addictive behavior in a geriatric patient with no prior history of addiction and significant **pain**.39

General guidelines for the use of opioids to treat PHN include the use of long-acting agents that provide consistent plasma levels to maximize **pain** relief and minimize adverse effects. Compound preparations (generally containing acetaminophen or aspirin) should virtually never be used because the added acetaminophen or aspirin does not help PHN and has the potential for inadvertent administration of toxic doses. Among long-acting opioids, methadone stands out for its low cost. In many states, methadone prescriptions need to be written "for **pain**" since pharmacies do not dispense methadone for treatment of addiction. Many supposed allergic reactions to opioids, such as nausea or sedation, reflect too-rapid administration and occur during the first week of use. Starting opioid treatment with low doses and only increasing as tolerated can avoid considerable distress. Constipation is the most common persistent adverse effect, but one that can usually be managed if discussed and treated. Some patients with good relief but persistent drowsiness from opioids (or any other medication) may do well if a second agent such as methylphenidate or desipramine is added to minimize drowsiness.

As always, use of opioids requires special consideration in geriatric patients, particularly since opioids are becoming a first-line option for the treatment of PHN in the elderly. Constipation and sedation need to be guarded against. In general, because of pharmacokinetic factors, lower doses are advisable, and sometimes use of a shorter-acting opioid that is more rapidly metabolized may be appropriate. The lowest available doses of some opioid medications (such as oxycodone HCl controlled-release, 10 mg) may be too high for a frail geriatric patient. In this setting, I particularly recommend a trial of tramadol37 (a mild mu-agonist and adrenergic reuptake inhibitor), because the 50-mg elongated tablets can be broken into halves or quarters, or methadone, whose 5-mg tablets can be similarly divided to give doses as low as 1.25 mg. While liquid preparations can also help in achieving small doses, there is the potential for inadvertent mismeasuring.

10. Are there any treatments that can be applied directly to the painful area?

Topical therapies are those that are applied directly to the painful area and act locally, without major systemic side effects. These must be distinguished from systemic medications that can be applied through the skin, such as fentanyl. Topical treatments are particularly attractive for use with geriatric patients who may already be taking several systemic medications and have increased risk of adverse effects. However, topical capsaicin, which is available over the counter for the treatment of PHN and has some evidence for efficacy,40 is poorly tolerated by

most patients due to intense burning upon application. Because of its neurotoxic effects on cutaneous axons,41 it is no longer considered to have sufficient efficacy and low-enough risk to be a first-line treatment for PHN. Some have advocated the use of aspirin dissolved in ether as a topical treatment for PHN,42 but this is not commercially available in the United States.

Fortunately, in recent years topical local anesthetics have been shown to be both effective and safe for treatment of PHN, particularly for the symptom of allodynia (pain from light touch). Of current interest is the lidocaine patch, approved by the FDA specifically to treat PHN. The patch has not only a pharmacologic benefit, but also shields the painful area from inadvertent contact.43,44 Systemic absorption is negligible when patches are applied to intact skin, and the only common side effect is cutaneous irritation in patients sensitive to any component of the patches. Other formulations of topical local anesthetics can be useful, including the application of lidocaine creams under occlusive plastic wrap.45-48 Viscous lidocaine dripped into the ear canal may help patients with Ramsay Hunt (VII cranial nerve) syndrome.

11. What should I do if my initial treatment doesn't seem to be working?

The most important determination is whether the first treatment has been given an adequate trial. In general, efficacy (or lack thereof) cannot be determined until a medication has been given enough time to work and administered at a high-enough dose. The definition of a high-enough dose is either the maximal tolerated dose (a higher dose produces intolerable adverse effects) or a dose corresponding to the typical adult dose (see Table for specifics). If a first-line therapy has been given an adequate trial and does not provide significant relief, it should be discontinued. Except for opioid medications, most of the therapies for PHN can be stopped with just a few days' taper. Even opioids are usually easily weaned by having patients reduce their dose by one-third to one-half, once or twice a week. Surprisingly, quite a few patients discontinue opioids abruptly on their own if they are ineffective or poorly tolerated, and do not report any withdrawal symptoms, providing further evidence of neurochemical disparities between use of opioids for analgesia and drug addiction.

The warning not to discontinue gabapentin abruptly applies primarily to patients with epilepsy in whom abrupt discontinuation of any anticonvulsant might precipitate seizures. When antiepileptics are used for pain management in people with no history of epilepsy, abrupt discontinuation will usually be safe, although discontinuation over at least a week is recommended for maximum safety. Sometimes abrupt discontinuation provokes worsening of the pain, letting the patient and physician know that the medication was in fact effective and should be resumed. If pain is no worse after a medication has been discontinued, do not resume that medication but move on to another treatment.

Sometimes patients experience partial pain relief from a medication but are hoping for more. This is the time to consider adding a second treatment. A second added medication should almost always be from a different class than the first. Different medications have different mechanisms of action and may potentiate each other. In this regard, treatment of PHN is similar to that of other serious chronic illnesses such as diabetes, hypertension, or asthma. Fortunately, the four classes of medications recommended for treatment of PHN can be taken simultaneously. Design of clinical trials needs to correspond better to real-world situations, and certainly, most PHN patients evaluated by specialists will end up on more than one medication at the same time even though there are almost no studies of combination therapies.

12. What are other potential complications of shingles?

The varicella-zoster virus has an affinity for invading the walls of blood vessels as well as sensory ganglia, and recent MRI studies have shown that it invades the central nervous system far more often during zoster than previously appreciated.49 It is an occasional cause of stroke, meningitis, and vasculitis of the brain or spinal cord;50 these complications occur more often in immunosuppressed patients,51 who are also at higher risk for disseminated or persistent zoster.

A common shingles complication that has only rarely been reported in the literature is chronic focal itch. Patients report that this can be as disabling as the pain, and it appears to be more

resistant to treatment. Rare patients with postherpetic itch (PHI) scratch themselves to the point of severe injury because neural damage from shingles has robbed affected areas of protective **pain** sensation.52 PHI is more common after shingles on the head and neck than the torso or limbs.53 Clinical experience suggests that dementia can increase the probability of self-injurious scratching during PHI.

13. Which medications have been proven ineffective for treatment of PHN?

Unlike other chronic diseases of geriatric patients, lifestyle changes offer no benefit for PHN and other **neuropathic pain** syndromes. In general, maintaining an active schedule and continuing to engage in pleasurable activities are associated with better tolerance of chronic **pain** and less depression and disability, but diet and physical activity are not known to have any direct influence on the rate of neural healing. There is also no evidence for efficacy of alternative medical options such as acupuncture.54 Except for rare cases, there are no effective neurosurgical options (as discussed in detail at www.shingles.mgh. harvard.edu), and so medications remain the major option for patients with moderate or severe PHN **pain**.

It is important to know which medications have been proven ineffective (or unsafe) and to avoid them. For treating zoster lesions, there is no role for antibiotics, either systemic or topical, unless secondary infection develops. Topical local anesthetics should not be used if there are still active lesions because of the possibility of systemic absorption. While local anesthetic nerve blocks or epidural catheters may rarely be needed for **pain** management during severe zoster, there is no evidence that they protect against PHN. Interventions directed at modulating the autonomic nervous system (eg, sympathetic ganglion blocks) are not indicated because zoster erupts only in the **somatic**, but not autonomic, neural ganglia, and there is little or no sympathetic involvement in shingles and PHN.

While nonsteroidal anti-inflammatory drugs have not been formally tested for **pain** relief in acute zoster, there is a rationale for their use, since some zoster **pain** is due to acute inflammation and tissue death. However, this is not the case in established PHN. Corticosteroids and ACTh were for many years standard therapy for zoster.55 More recent controlled studies have not shown that corticosteroid use during zoster prevents PHN, and concerns have been raised about adverse effects relevant to geriatric patients such as glucose intolerance, osteoporosis, cognitive changes, and gastritis.56 My clinical practice is to limit use of steroids to situations in which swelling and inflammation in zoster-affected nerves can cause secondary damage (eg, during facial zoster when inflamed cranial nerves can be compressed when exiting the skull or when there is risk of paralysis from damage to motor axons passing through shingles-inflamed nerves).57

14. What is clinical experience with the use of intrathecal steroids to treat PHN?

In 2000, a blinded controlled trial in Japan documented outstanding **pain** relief after intrathecal administration of methylprednisolone and lidocaine to treat intractable PHN.58 However, concerns were raised about the safety of intrathecal administration of local anesthetics (which can cause profound hypotension or diaphragmatic paralysis), the potential for arachnoiditis, and the lack of the preservative-free methylprednisolone necessary for intrathecal administration. These concerns have inhibited attempts to formally duplicate this study in the United States. Clinical experience at several major PHN centers has not demonstrated the level of effectiveness reported, perhaps because of inability to exactly replicate the protocol.

Acknowledgments

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Visceral Pain and its Management • 14 RC 1

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Visceral **pain** is a frequent cause of referral for gastroenterological examinations [1]. It is the main symptom in illnesses such as myocardial ischaemia, upper gastrointestinal dyspepsia, irritable bowel syndrome and dysmenorrhea.

Visceral **pain differs** from **somatic pain**, because it is diffuse, difficult to localise and is referred to **somatic** areas [2]. As well as being referred to the body surface, several viscera can converge onto the same spinal segment. Therefore patterns of referred sensations overlap considerably, causing problems with differential diagnosis [3]. Visceral **pain** affects basic physiological functions such aseating and defaecation, and vagal activation causes fatique and anxiety.

Basic research into the mechanisms of visceral **pain** and nociception has increased greatly in the last decade [4,5]. Most visceral nociceptors are unmyelinated, polymodal C fibres. The innervation of viscera is sparse compared to **somatic** structures, giving rise to only about 10% of all afferent fibres. Silent visceral nociceptors have been found [6] whose nerve endings are activated during inflammation and probably in hyperalgesic **pain** states. Visceral hyperalgesia is a **pain** state caused by central sensitisation, that leads to abnormal perception of both painful stimuli (hyperalgesia) and non-painful stimuli(hyperaesthesia or if perceived as **pain**, allodynia). Long-lasting **pain** states, chronic inflammation, genetic factors and many unknown factors contribute to the generation of visceral hyperalgesia/ allodynia, and these have a fundamental role in chronic visceral **pain** states [7]. Temporal and spatial summation (the supra-additive effect of repeated or adjacent stimuli) is also important in the development of hyperalgesia[3]. As hyperalgesia develops, several changes take place in the central nervous system. These include increased activity in the glutamate system, especially activation of the NMDA-receptor complex, and increased concentrations of nociceptive substances such

as dynorphins, CGRP and Nerve Growth Factor (NGF)[8], causing increased sensitivity and reduced endogenous inhibition [9]. A persisting barrage of noxious stimuli onto the spinal cord can result in excitotoxicity causing cell death, especially of small inhibitory interneurons. Taken together, these changes result in constant hyperexcitability and can cause persistent **pain**, even though the primary cause has disappeared. A **pain** memory has developed [7]. **Somatic** hyperalgesia associated with visceral **pain** has been known for over 100 years [10]: attacks of angina pectoris are associated with persistent skin tenderness that remains after the attack. The importance of referred **somatic** hyperalgesia in response to visceral **pain** and hyperalgesia is currently being studied [11].

The treatment of visceral **pain** should try to remove or reduce the cause of **pain**. However, some **pain** states have no known cause, or are functional, or caused by intractable diseases, such as cancer, chronic inflammation or ischaemia. These patients can be referred to anaesthesiologists or **pain** clinics for treatment.

A major problem with visceral **pain**-treatment is that adverse reactions to analgesics include disturbed visceral function such as nausea, constipation, and gastric irritation and ulceration. This has to be taken into account when therapy is considered.

In general, the treatment of visceral **pain** follows the international guidelines for treatment of **somatic pain**. As long as the aetiology is known and nociception is present, as in cancer or inflammatory diseases, the **pain** will respond to treatment. The major clinical task is to adjust individual treatment with regard to effect and adverse effects. Constant visceral **pain** is treated with a combination of NSAID´s, paracetamol and opioids. Dosage is adjusted according to the patients report of **pain** relief, taking side effects into account.

Visceral **pain** states can include **neuropathic pain**, such as cancer patients with affection of peripheral nerves or **neuropathic pain** following surgery, for example phantom rectum sensations and **pain**. A thorough history and assessment of the **pain** is necessary. If **neuropathic pain** is suspected, it should be treated with either antidepressants or anticonvulsants [12,13]. Depending on the patient response, and the cause and the type of **pain**, patients can receive up to four different kinds of analgesics, i.e. NSAID´s/paracetamol, opioids, antidepressants and anticonvulsants. This type of treatment is a therapeutic challenge and needs careful monitoring.

An advantage of **pain** clinics is the opportunity to listen to what the patients feel about their **pain**, and carefully follow the effects of treatment so that efficacy and adverse effects can be balanced. The effects of different analgesics listed in table 1.

Table 1: Effect of different drugs on different categories of visceral pain

	NSAID/PCT	Opioids	Anti-depressants	Anti-convulsants	smooth muscle relaxants
Acute	+	+	-	-	(+)
Cancer	+	+	+	+	(+)
Chronic	+	-/(+)	+	+	+
constant/ nociceptive	+	+	-	-	(+)
Dysaesthesia	(+)	(+)	+	+	-

Neuralgia	(+)	(+)	+	-	+
Colic	(+)	(+)	+	-	+
Functional/- visceral hyperalgesia	+	(+)	+	-	+

effect:: +; *doubtful effect*: (+); *no effect or relatively contraindicated*: -; *PCT*: paracetamol

Evidence of their activity against visceral **pain** is limited, and usually based on clinical experience and the **somatic pain** literature.

An important future challenge is the treatment of visceral functional disorders, such as dysmenorrhea, non-peptic dyspepsia, non-cardiac chest-**pain** and irritable bowel syndrome. These conditions are widespread, with a prevalence of up to 20 % in the community[7]. The discovery that visceral hyperalgesia has a prominent part in the cause of these syndromes is encouraging and suggests future means of treatment. Antidepressants [14,15] and peripheral kappa opioid agonists [16,17] have shown promising results in clinical studies. Basic and applied pharmacological research in this field is intense. The use of agents such as kappa and peripherally acting opioids, $5\text{-}HT_{3,4}$ antagonists, SSRIs or other possible visceral analgesics await further study.

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7

Visceral Pain Mechanisms

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That visceral **pain differs** significantly from other types of pains has been appreciated by clinicians for centuries. As recently as the turn of this century, however, investigators were in disagreement about the source(s) of visceral **pain**. Lennander (24) and MacKenzie (28) maintained that **pain** was not derived directly from a viscus (see discussion in ref. (25)), whereas others provided evidence for what they called ``true visceral **pain**'' or ``splanchnic **pain**'' ((43); discussion in ref. (25)). The issue is no longer contentious, but its consideration emphasizes several points important to our current understanding of visceral **pain**. First, **pain** per se does not arise from all viscera (e.g., liver parenchyma), but **pain** associated with such viscera does arise when the capsule containing that viscus distends or becomes inflamed. Second, tissue injury (or threat of such injury) may not be required or necessary for production of visceral **pain**, as it is for **pain** from cutaneous structures (see refs. (6) and (37) for discussion). Thus, unlike cutaneous **pain**, the adequate stimuli for production of visceral sensation, including **pain**, are not yet fully appreciated.

CHARACTERISTICS OF VISCERAL PAIN

A number of characteristics of visceral **pain** are widely appreciated (Table 1). These characteristics have been reviewed previously (6,37) and only a few additional comments will be made here. Localization of the source of visceral **pain** is understood to be confounded by its referred nature. It should also be appreciated that in addition to referral to cutaneous structures, multiple viscera often converge onto the same spinal cord neurons. Thus, patterns of referred sensation from the gallbladder, esophagus, and heart or from the urinary bladder and colon overlap considerably, creating obvious problems with respect to differential diagnoses. That a cutaneous hyperalgesia is often associated with visceral **pain** is also not fully appreciated. More than 100 years ago, Sturge (45) noted that attacks of angina are associated with a persistent cutaneous tenderness that remains after the attack (discussed in ref. (25)). MacKenzie (28) and Head (19) both described hyperalgesia of the skin on the head and neck associated with toothache and diseases of the ear, tongue, and nose, and neither investigator apparently considered that **somatic** or visceral sources produced different forms of hyperalgesia. More recently, Hardy et al. (17) documented the development of cutaneous hyperalgesia after both deep **somatic** noxious stimulation (6% saline injected into one side of an intraspinous ligament, which produced an ``intense aching **pain**'') (Figure 1) and visceral stimulation (subphrenic irritation with bubbles of CO), which differed in

no significant way from hyperalgesia secondary to an experimental skin injury. These investigators commented that, as regards the properties of cutaneous hyperalgesia, ``it makes little difference whether the source be from the skin, from deep **somatic** structures or from a viscus'' (17). These and other similar observations have considerable importance with respect to understanding central mechanisms of altered sensations that arise from deep structures (see below). In passing, it is interesting to note that Lewis (25) and Hardy et al. (17) differed in their interpretation of the mechanisms that lead to the development of hyperalgesia (secondary hyperalgesia), which seem clear today to be central in origin,

not peripheral.

Chapter 7 Table 1: Characteristics of visceral pain

Referral/transferral to cutaneous structures
Diffuse and difficult to localize
Enhanced autonomic and/or motor reflexes
Cutaneous and deep tissue hyperalgesia

ADEQUATE VISCERAL STIMULI

Although the adequate stimuli for visceral **pain** are not fully understood, a variety of natural stimuli are clearly associated with **pain** from the viscera (Table 2). Experimentally, mechanical stimuli such as traction of the mesentery, stretch of serosal tissues, compression of organs, and particularly distention of hollow organs produce **pain** in humans and nonhuman animals.

Chapter 7 Table 2: Naturally occurring visceral stimuli

Hollow organ distention
Ischemia
Inflammation
Muscle spasm
Traction

Because many hollow organs are easily accessible and distention reproduces a natural stimulus that produces **pain** in humans, there is a rich clinical literature of studies investigating sensation arising from the gastrointestinal tract. For example, Payne and Poulton (40) distended their own esophagi, describing **pain** as ``continuous and burning'' at lesser volumes/pressures and ``gripping'' at the greatest volumes/pressures tested. Their **pain** was referred from the area of the suprasternal notch to the xiphoid process and sometimes to the costal angle, with radiation to the angle of the left scapula. Painful distentions also produced alterations in the pattern of breathing, and these investigators also experienced cutaneous hyperesthesia in the skin over the sternum. In an examination of the sensibility of the sigmoid colon and rectum, Goligher and Hughes (14) found that the sensation of **pain** was related to the pressure within the distending balloon rather than the volume of the balloon. They also made a distinction in their studies between colonic sensation and rectal sensation, suggesting that the former was **pain** carried by afferents in the sympathetic nerves and that the latter was fullness carried by afferents in the pelvic nerve.

The first investigators to employ controlled, constant pressure stimuli in studies of sensation from the gut were apparently Lipkin and Sleisinger (26). Using balloons to distend the esophagus, ileum, or colon, they documented that the latency from the onset of the stimulus to patient reports of **pain** was directly related to the intensity of the distending stimulus. At lesser distending pressures, they found that the stimulus was not reported by subjects as painful for up to 1 min after the onset of distention and was preceded by the sensation of pressure over large abdominal or thoracic areas. They determined in their studies that the minimal intraluminal pressures to produce painful sensations from the esophagus, ileum, and colon were 39 to 47, 44 to 59, and 40 to 50 mm Hg, respectively. A more complete description of such studies is available elsewhere (37). With respect to distention of hollow organs, Lewis (25) commented earlier that distention of the gut was most painful when long, continuous segments of the gut were simultaneously distended. Even greater pressures within smaller segments of the gut were not as efficacious in producing painful sensations. Thus, spatial summation is clearly an important contributor to visceral **pain** mechanisms.

Inflammation or ischemia of a viscus generally leads to altered sensations from the viscus, including **pain**. The example of Wolf's patient Tom is instructive (49). When Tom's stomach mucosa was ``normal,'' neither pinching a fold

of mucosa with a forceps nor electrical stimulation of the mucosa, applied at an intensity sufficient to cause ``intense **pain** in the tongue,'' was painful. However, after the mucosa was rendered ``red, boggy and edematous'' by application of powdered mustard after removal of the mucus, intense **pain** occurred with application of these same stimuli to the now inflamed tissue. This should not be surprising and is in some ways analogous to the hyperalgesia associated with inflammation of cutaneous structures.

Interruption of the blood supply to most deep structures, including the viscera, also frequently leads to **pain** (e.g., myocardial ischemia). Experimentally, occlusion of the blood supply to the colon increases significantly the rates of spontaneous and contraction-related discharges of afferent fibers from the colon (18). Other investigators have examined the effects of ischemia/anoxia on abdominal afferents (gallbladder, pancreas, mesentery, and liver [27]) and cardiac afferents (2,4). In general, although ischemia/anoxia may reproduce a stimulus that arises naturally, occlusion of blood supply to an organ is not a stimulus generally well suited to stimulus-response experimental investigation; ischemia/anoxia is, however, a useful ``conditioning'' stimulus. Like ischemia/anoxia, inflammation also reproduces a visceral stimulus that arises naturally but is similarly associated with changes in experimental parameters only after a relatively long latency. Thus, although ischemia and inflammation are important clinically, they are better suited experimentally to condition organs and thus responses to stimuli delivered to them (e.g., mechanical distentions).

VISCERAL AFFERENTS

The anatomical organization and central termination of afferent fibers that convey information from the viscera to the central nervous system are well understood, even though their adequate stimuli are not. Visceral afferents ``run'' with sympathetic and parasympathetic efferent nerves. It has long been considered that only so-called sympathetic afferents (i.e., visceral afferent fibers running with sympathetic nerves), with cell bodies in dorsal root ganglia, convey nociceptive information from viscera to the central nervous system. This notion is incorrect, and it is clear, for example, that urinary bladder and colonic afferents in the parasympathetic pelvic nerve transmit nociceptive information (21,35), and it is also likely that some afferents from thoracic and upper abdominal organs contained in the vagus nerve also subserve a nociceptive function. Thus, the viscera, in general, receive a dual innervation with afferents reaching the spinal cord (cell bodies in dorsal root ganglia) or brain stem (cell bodies in nodose ganglion) via sympathetic and parasympathetic nerves.

Visceral afferents terminate in the spinal dorsal horn in superficial laminae (I and IIouter) and the neck of the dorsal horn in lamina V; visceral afferent fibers also terminate in the area around the central canal (often called lamina X). It is interesting to note that, whereas **somatic** afferents terminate throughout the spinal dorsal horn (i.e., laminae I-VI), cutaneous *nociceptors* terminate in the spinal dorsal horn in a pattern similar to visceral afferents: superficial dorsal horn and neck of the dorsal horn.

The functional classification of visceral afferents has been an issue of some disagreement. Some visceral afferents (e.g., biliary system, colon, ureter) have high mechanical thresholds for activation, respond only to apparently noxious intensities of stimulation, and encode the intensity of stimulation in this noxious range (5,18) (see Figure 2);

these afferents are analogous to those from skin classed as nociceptors and thus appear to subserve a similar nociceptive function from the viscera. A greater proportion of visceral afferents, however, have thresholds for activation in the physiological range and encode the intensity of stimulation throughout the non-noxious and noxious ranges of stimulation (1,21). Some of these afferents also respond to several modalities of stimulation (e.g., mechanical, chemical) (22) and thus may be similar to polymodal afferents from cutaneous structures, although these visceral afferents also respond to presumably non-noxious intensities of stimulation. Several factors likely contribute to our present inability to classify visceral afferents (as cutaneous afferents have been categorized; see ref. 48). First, the issue of the adequate stimulus contributes to the problem; moreover, such stimuli are certainly different for different organs (e.g., mechanical distention of the colon versus ischemia of the myocardia vs inflammation of the urinary bladder). Second, most studies have been done using only a limited array of test stimuli because, experimentally, it is not generally an easy matter to apply a wide range of different stimuli to often difficult-to-access viscera. Although clinical evidence suggests that **pain** arising from one viscus is similar, if not identical, to **pain** arising from other viscera in terms of intensity and quality, this does not address the issues above, but simply emphasizes that our interpretation of

the sensation is consistent.

Another point to be emphasized is that the number of visceral afferents, relative to the number of afferents from cutaneous structures, is very small. The number of visceral afferents has been variously estimated to be between 2% and 10% of all afferents to the spinal cord (depending on the spinal level of input) (7,12,21). This low number is significantly out of proportion to the relative number of spinal dorsal horn neurons that respond to visceral stimulation in those same spinal segments, estimated to be 50% to 75% (10). This discrepancy is apparently explained by the significantly greater rostrocaudal spread of visceral afferent terminals in the spinal cord than the rostrocaudal spread of the more numerous cutaneous afferent terminals (46).

Further, in studies in which visceral afferents have been found by electrical stimulation, a surprising proportion have been found to not be responsive to the stimuli tested (typically mechanical). Afferents from the joint first found in this manner have been dubbed ``sleeping" or ``silent" afferents, awakening only after experimental inflammation of the joint (44). Similarly, irritation/inflammation of the urinary bladder has been shown to lead to increased responses to mechanical stimulation of unmyelinated pelvic nerve afferents that previously gave only weak or no responses to the same mechanical stimuli before inflammation of the bladder (16). It is now apparent that there exists a new and large group of nociceptors from **somatic** and visceral structures that play an important role in nociception after tissue is inflamed or injured. Accordingly, irritation/inflammation has been employed experimentally in a variety of studies to ``condition" responses to visceral stimuli. For example, responses of spinal dorsal horn neurons to distention of the urinary bladder or noxious colorectal distention are greater after irritation of these organs with 25% turpentine (30,37). Importantly, behavioral responses of rats also are significantly influenced by prior conditioning of the colon with turpentine. For example, colorectal distention at intensities of 30 mm Hg or less produce no change in rats' behavior in a passive avoidance paradigm (i.e., these intensities are not noxious), but 30 mm Hg colorectal distention does lead to acquisition of the avoidance behavior after conditioning of the colon with turpentine (39).

As a result of increased interest and investigation into mechanisms of visceral **pain**, including the discovery of silent afferents and the use of conditioning stimuli that more closely approximate clinical situations, our thinking about visceral **pain** is undergoing rapid change. Whether there exist specific visceral nociceptors is no longer at issue, because some afferents from visceral (as well as **somatic**) structures have been shown to acquire new response properties, including responses to noxious stimuli, when tissue is injured or inflamed. Thus, some visceral afferents may function in all conditions to convey nociceptive information (e.g., from gallbladder or ureter), whereas afferents from other viscera undergo a change in their sensitivity to applied stimuli after irritation/inflammation of a viscus (i.e., previously silent afferents become active/responsive). In the clinical circumstance, in which irritating and/or inflammatory conditions are common, visceral nociceptors are likely active.

It should be emphasized, however, that whereas many afferents from a viscus may become active during an experimentally induced inflammation and presumably in disease (e.g., pancreatitis, malignancies), investigators are not at present able to account for the function(s) of a significant number of afferents that cannot be activated by any stimuli tested, even after irritation/inflammation of the organ. This is a recently appreciated situation, best exemplified by the work of J;auanig and colleagues (15,16). They studied unmyelinated afferent fibers innervating the pelvic viscera in cats and found that less than 10% of the afferents in the pelvic nerve could be activated by noxious mechanical distention of the urinary bladder. They also described a small number of unmyelinated afferents that were chemosensitive (mustard oil or turpentine), some of which acquired mechanosensitivity after inflammation of the bladder by these irritants. Thus, there remain a very large number of unmyelinated afferents in the pelvic nerve (perhaps as much as 90% of the total) for which no function is apparent. Extrapolating from these investigations, for which adequate stimuli were identified for a small number of afferent fibers, an obvious conclusion is that adequate stimuli have not been identified for the majority of visceral afferents in the body. Clearly, not all visceral afferents need play a role in sensation, and perhaps some of these ``unresponsive" visceral afferents are important to other functions (e.g., monitoring gut or bladder content by sensitivity to pH, nutrients, gases, and various ions). Further, it is not to be expected that the relatively acute irritation/inflammation produced experimentally reproduces the clinical circumstance in which such insults are generally slower in onset and longer in duration. That is, it may be that more afferents are ``recruited" into function over time as the severity of the insult progressively worsens.

VISCERAL HYPERALGESIA

Finally, there is considerable evidence now accumulated that indicates that altered central mechanisms play an important role in visceral sensations. It has been well established in peripheral, cutaneous models of tissue injury or inflammation that secondary hyperalgesia and central sensitization contribute to the altered sensations arising from the area of the insult. Two alterations are prominent: previously non-noxious stimuli (e.g., brushing of the skin) applied to the area now produce **pain** (i.e., the phenomenon of allodynia) and responses to threshold intensities of noxious stimuli are greatly enhanced (i.e., the phenomenon of hyperalgesia). There is no reason to expect that similar mechanisms of hyperalgesia and central sensitization do not also obtain from visceral organs and may be important to a variety of clinical problems of altered sensations from the viscera.

Experimentally, evidence for one or more altered central mechanisms is provided by changes in the size of receptive fields of spinal dorsal horn neurons after some conditioning stimulus. Hylden et al. (20) documented that inflammation of a hindpaw of the rat led to a significant increase in the size of convergent, cutaneous receptive fields of spinal neurons studied in dorsal horn lamina I. Also in the rat, the cutaneous receptive fields of spinal dorsal horn neurons have been shown to increase in size after repetitive esophageal distention (Figure 3), repetitive gallbladder distention (8), and repetitive colorectal distention (figure 4). That these convergent, cutaneous receptive fields expand in size after repetitive distention of a viscus unquestionably implicates one or more central mechanisms, because there is no convincing evidence for the existence of a large number of bifurcating or dichotomizing neurons that simultaneously innervate a cutaneous structure and a viscus. Thus, the repetitive visceral input to the dorsal horn must alter the excitability of central neurons, leading to several changes, including a significant increase in the size of the receptive field from the convergent cutaneous input. Repetitive colonic distention in humans similarly leads to an increase in the area of referred sensation and also to a change (increase) in the reported qualities of the stimulus (38). In these experiments, 10 consecutive distentions (60 mm Hg given 4 min apart) lead to an obvious and significant increase in the areas of referred sensation (Figure 5A). Comparing visual analog scale ratings during the first and last of the 60 mm Hg distentions also reveals that the stimulus was considered painful at the end of the series of distentions, whereas it was not uniformly considered to be painful during the first distention (Figure 5B). Analysis of verbal descriptors of the quality of the sensation produced by sigmoid colon distention also revealed that subjects reported a significant increase in the magnitude of the descriptors selected for the sensations produced (38).

In continuing electrophysiological investigations in the rat, the convergent, cutaneous receptive fields that increased in size after repetitive colonic distention were found to further increase in size after conditioning of the colon with 25% turpentine. It is interesting to note in figure 4 that the convergent, cutaneous fields, after instillation of turpentine into the colon, grew to include the contralateral side of the rats' dorsal body; converging, cutaneous receptive fields in untreated rats never included an area on the contralateral body surface (36). These results suggest that two different mechanisms may be operative, because there appear to be two stages to the increase in size of convergent, cutaneous receptive fields. It is possible that the receptive field would continue to grow with repeated colorectal distention to the size finally determined after treatment with turpentine. Results to date, however, suggest that receptive fields increase in size during repetitive colorectal distention over the course of 1 to 2 hr and do not increase further. Therefore, it seems likely that an additional mechanism is engaged by the chemical insult (e.g., recruitment of previously silent afferents from the colon and enhanced excitability of a greater number of dorsal horn neurons than affected by repetitive colorectal distention alone). It is understandable, on the basis of such results, why patients' complaints of **pain** increase over time.

In a recent review (29), it was suggested that a number of visceral disorders (e.g., noncardiac chest **pain**, nonulcer dyspepsia, irritable bowel syndrome) may be reflections of a form of visceral hyperalgesia and/or may involve

mechanisms analogous to **neuropathic** conditions. In support, there are a number of clinical observations of lowered **pain** thresholds in response to distention of hollow organs (esophagus, stomach, and colon) in some of these patients (23,41,42). In general, these studies find that normal visceral sensations are experienced in these patients at reduced distending pressures. It has been known for some time, for example, that individuals with irritable bowel syndrome have reduced thresholds to colonic distention and report a greater incidence of **pain** associated with distention than do normals (42) (Figure 6). Further, the area of referred sensation in normals and patients with irritable bowel syndrome clearly differ (47) (Figure 7). These clinical observations complement the experimental results briefly described above, suggesting that central mechanisms best understood in cutaneous models of hyperalgesia and central sensitization likely also explain altered sensations from the viscera.

Central sensitization refers to alterations in the excitability of spinal cord neurons to a variety of normal inputs following peripheral tissue damage or irritation (50). Central sensitization is manifest as a prolonged facilitation of reflexes and an increase in receptive field size of dorsal horn neurons (e.g., see Figs. 3 and 4 and ref. 50).

The central mediators involved in the development of central sensitization are incompletely understood at present. The release of neuropeptides (e.g., substance P, calcitonin gene-related peptide) from the central terminals of primary afferent fibers appears to play an important role, as does activation of the N-methyl-d-aspartate (NMDA) receptor (11,51). Most recently, a role for nitric oxide (NO) in NMDA-receptor-mediated facilitation of a nociceptive reflex (33) and in the thermal hyperalgesia produced in experimental models of hind limb inflammation and **neuropathic pain** in the rat has been suggested (34; Meller, Cummings, Traub, and Gebhart, *unpublished*). NMDA receptor activation results in an influx intracellularly of calcium that, acting at a calmodulin site on NO synthase, leads to the production of NO (or an NO-containing moiety) (13). NO is a small, rapidly diffusible molecule that is believed to escape from its site of synthesis and act as a ``retrograde" messenger in the presynaptic terminal or to influence activities in adjacent neurons and/or glia (see ref. 32 for a recent review relative to NO and nociception). NO ultimately leads to the production of cGMP, which has well-documented second messenger functions.

The theme of visceral hyperalgesia and its ability to explain many of the clinical features of noncardiac chest **pain**, nonulcer dyspepsia, and irritable bowel syndrome patients is discussed in detail elsewhere (29). A further analogy considered in greater detail elsewhere (29) is that between **neuropathic** or sympathetically maintained pains and unknown insult to a ``visceral" nerve. It is possible that an initiating insult, which would likely be minor and may even be missed, could produce persistent, altered sensations arising from a viscus, including **pain**. Campbell and colleagues have offered a unifying hypothesis to explain sympathetically maintained **pain** (3). They suggest that sympathetically maintained **pain** is a receptor disorder and that activity in cutaneous nociceptors leads to an up-regulation of adrenoceptors on the terminals of the nociceptors. If this is the case, the phentolamine test advocated by Campbell and colleagues could be useful in determination of whether a circumstance analogous to sympathetically maintained **pain** is associated with viscera.

SUMMARY

Our understanding of visceral **pain** mechanisms has advanced appreciably over the past several years. The cutaneous hyperalgesia associated with visceral **pain** and the central mechanisms likely associated with expansion of receptive fields/areas of referral appear to be analogous to those better studied from cutaneous structures. That repeated visceral stimulation or irritation/inflammation of a viscus may awaken silent nociceptors has helped understand how **pain** sensation likely increases as disease processes progress. Thus, we may now consider visceral hyperalgesia as a common factor among a number of visceral disorders, many previously poorly classified as motility disorders (29). This hypothesis requires testing, but appears to be reasonable in light of experimental evidence obtained from nonhuman animals.

There remain, however, some unresolved issues. Foremost among them is the function of what is apparently the majority of visceral afferent fibers. It may be that all afferents from some organs have an identified function, but it

appears that afferents from much of the viscera have no function yet associated with them. It seems unlikely that all visceral afferents are associated with sensation, and many may be associated with other aspects of visceral function, including reflex functions and monitoring visceral content. Often not considered are possible functions of visceral afferents associated with local, trophic modulation of a viscus (31). As investigators identify adequate stimuli for visceral afferents, appreciating that it is likely that these adequate stimuli are different for different viscera, our understanding of visceral sensation, and particularly visceral **pain**, will improve and perhaps suggest improved treatment for **pain** control.

ACKNOWLEDGMENTS

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Behavioral/Systems/Cognitive

Reduced Nerve Injury-Induced Neuropathic Pain in Kinin B$_1$ Receptor Knock-Out Mice

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Injury to peripheral nerves often results in a persistent neuropathic pain condition that is characterized by spontaneous pain, allodynia, and hyperalgesia. Nerve injury is accompanied by a local inflammatory reaction in which nerve-associated and immune cells release several pronociceptive mediators. Kinin B$_1$ receptors are rarely expressed in nontraumatized tissues, but they can be expressed after tissue injury. Because B$_1$ receptors mediate chronic inflammatory painful processes, we studied their participation in neuropathic pain using receptor gene-deleted mice. In the absence of neuropathy, we found no difference in the paw-withdrawal responses to thermal or mechanical stimulation between B$_1$ receptor knock-out mice and 129/J wild-type mice. Partial ligation of the sciatic nerve in the wild-type mouse produced a profound and long-lasting decrease in thermal and mechanical thresholds in the paw ipsilateral to nerve lesion. Threshold changed neither in the sham-operated animals nor in the paw contralateral to lesion. Ablation of the gene for the B$_1$ receptor resulted in a significant reduction in early stages of mechanical allodynia and thermal hyperalgesia. Furthermore, systemic treatment with the B$_1$ selective receptor antagonist des-Arg^9-[Leu^8]-bradykinin reduced the established mechanical allodynia observed 7–28 d after nerve lesion in wild-type mice. Partial sciatic nerve ligation induced an upregulation in B$_1$ receptor mRNA in ipsilateral paw, sciatic nerve, and spinal cord of wild-type mice. Together, kinin B$_1$ receptor activation seems to be essential to neuropathic pain development, suggesting that an oral-selective B$_1$ receptor antagonist might have therapeutic potential in the management of chronic pain.

Key words: neuropathic pain; allodynia; hyperalgesia; B$_1$ receptor; kinin; bradykinin

Introduction

Injury to a peripheral nerve in humans often results in a persistent neuropathic pain condition that is characterized by spontaneous pain, allodynia (pain responses to non-noxious stimuli), and hyperalgesia (exaggerated pain responses to noxious stimuli) (Malmberg and Basbaum, 1998). This type of chronic pain differs substantially from acute pain not only in terms of the persistence of pain but also with regard to the maladaptive changes, such as neuroplasticity, that have been described at various levels of the nervous system (Besson, 1999). Thus, the available analgesic drugs often have limited therapeutic value in the management of chronic pain and they may, in fact, represent a risk to the patient because of their common side effects (Woolf and Mannion,

1999). Therefore, the development of safe and efficacious drugs to treat chronic pain is an urgent priority.

Nerve injury is accompanied by a local inflammatory reaction in which nerve-associated and immune cells release several pronociceptive mediators such as cytokines, eicosanoids, and kinins (Tracey and Walker, 1995; Bennett, 1999). Of note, increased serum bradykinin levels have been found in patients with neuropathic pain (Blair et al., 1998).

Kinins are peptides formed in plasma and peripheral tissues in response to the activation of a class of enzymes, denoted "kallikreins," on kininogen substrates. Kinins are involved in a wide range of physiological mechanisms, including control of blood pressure, smooth-muscle contraction or relaxation, vascular permeability, and pain transmission. Furthermore, kinins are implicated in pathological states such as arthritis, pancreatitis, and asthma (for review, see Calixto et al., 2000, 2004). The actions of kinins are mediated through the stimulation of two subtypes of G-protein-coupled receptors, denoted B$_1$ and B$_2$. The kinin B$_1$ receptors exhibit higher affinity for the carboxypeptidase metabolites of kinins, des-Arg^9-bradykinin and des-Arg^{10}-kallidin. Usually, the B$_1$ receptors are hardly expressed in nontraumatized tissues, but they can be expressed under certain conditions, such as those after tissue injury and infection (for review, see Marceau et al., 1998). In contrast, the B$_2$ receptors for which bradykinin and kallidin exhibit great affinity are usually constitutively ex-

pressed and widely distributed throughout central and peripheral tissues (for review, see Calixto et al., 2000, 2004).

Once formed in the periphery, kinins activate Aδ and C fibers in sensory nerves producing pain, hyperalgesia, or allodynia in both humans and experimental animals. In addition, kinins may cause the release of other mediators such as neurokinins, calcitonin gene-related peptide, nitric oxide, and arachidonic acid metabolites, which also account for primarily their proinflammatory and nociceptive properties (for review, see Calixto et al., 2000, 2004) (Dray and Perkins, 1997).

Recently, the use of both B$_1$ and B$_2$ knock-out mice has led to a better understanding of the role played by kinins in physiological and pathological processes (Borkowski et al., 1995; Pesquero et al., 2000). For example, the deletion of the B$_1$ receptor gene significantly decreases acute and chronic inflammatory nociception (Pesquero et al., 2000; Ferreira et al., 2001, 2002). In the present study, we examine the contribution of the kinin B$_1$ receptor to the chronic nociception produced by peripheral nerve injury using knock-out mice, selective drugs, and the measurement of mRNA levels.

Materials and Methods

Animals. Experiments were conducted using male and female wild-type 129/J mice and kinin B$_1$ receptor knock-out mice (20–30 g; 129/J background) kept at controlled room temperature (22 ± 2°C) under a 12 h light/dark cycle (lights on at 6:00 A.M.) and 60–90% humidity. The animals were obtained from the Department of Biophysics at the Federal University of São Paulo (Brazil). Deletion of the entire coding sequence for the kinin B$_1$ receptor was achieved as described previously (Pesquero et al., 2000). The experiments were performed in accordance with current guidelines for the care of laboratory animals and ethical guidelines for the investigation of pain in conscious animals (Zimmermann, 1983). The number of animals and intensity of noxious stimuli used were the minimum necessary to demonstrate the consistent effects of drug treatments or genetic manipulation.

Partial sciatic nerve ligation. For the induction of chronic neuropathy, male and female mice were anesthetized by intraperitoneal injection of 7% chloral hydrate (0.6 ml/kg; Vetec, Rio de Janeiro, Brazil). A partial ligation of the right sciatic nerve was made by tying one-third to one-half of the dorsal portion of the sciatic nerve, using a similar procedure to that described for rats by Seltzer et al. (1990) and for mice by Malmberg and Basbaum (1998). In sham-operated mice, the nerve was exposed without ligation.

Measurement of thermal hyperalgesia. Thermal hyperalgesia was measured using the paw-withdrawal latency according to the method described by Hargreaves et al. (1988), with minor modifications. After challenge, hyperalgesia was measured at several time points after nerve injury (1–42 d), as described below. Thermal baseline measures were obtained from nonoperated animals 1 d before nerve injury. Mice were placed in clear plastic chambers (7 × 9 × 11 cm) on an elevated surface and allowed to acclimatize to their environment for 1.5 h before testing. The heat stimulus was directed to the plantar surface of each hindpaw in the area immediately proximal to the toes. The infrared intensity was adjusted to obtain basal paw-withdrawal latencies of ~11 s. An automatic 20 s cutoff was used to prevent tissue damage.

Measurement of mechanical allodynia. Mechanical nociceptive thresholds in mice were measured as the withdrawal response frequency to application of von Frey hairs (Stoelting, Chicago, IL). Six hairs with forces of 0.07, 0.16, 0.6, 1, 2, and 4 g were applied 10 times each to the plantar surface of each hindpaw following an alternating sequence and in ascending order of force. The monofilament was applied at intervals of 2 s to slightly different loci on the plantar surface of both hindpaws. A positive withdrawal response was considered valid only when the hindpaw was completely removed from the platform. The frequency of positive responses was calculated after 10 applications of the filament. The frequency of response was measured before and 1–42 d after nerve injury. Mechanical baseline measures were obtained from nonoperated animals

1 d before nerve injury. Mice were placed individually in clear Plexiglas boxes (9 × 7 × 11 cm) on elevated wire mesh platforms to allow access to the ventral surface of the hindpaws. Animals were acclimatized to the testing chambers, and the static mechanical withdrawal threshold was determined before and after nerve injury. The involvement of the B$_1$ receptor in mechanical allodynia was tested by using the selective antagonist of the B$_1$ receptor des-Arg^9-[Leu^8]-bradykinin (150 nmol/kg, s.c.; Sigma, St. Louis, MO) (Ferreira et al., 2001).

Quantitative real-time PCR. The expression of B$_1$ receptor mRNA was measured using a quantitative real-time PCR according to the method described previously (Argañaraz et al., 2004). Several days after nerve lesion, mice ($n = 3$–6 for each group) were killed, and the plantar skin of the right hindpaw, right sciatic nerve, dorsal portion of spinal cord, and whole cerebral cortex were isolated, dissected, and frozen in liquid nitrogen and stored at −80°C. Thawed tissue was homogenized in 0.3–1 ml of TRIzol reagent (Invitrogen, Gaithersburg, MD), and total RNA was isolated according to the instructions of the manufacturer. Before cDNA synthesis, RNA samples were pretreated with DNase I (Invitrogen) to avoid genomic DNA contamination. Reverse transcription was performed using 2 μg of total pure RNA, 50 ng of random hexamer primers, and 200 U of Maloney murine leukemia virus reverse transcriptase (Invitrogen), as described by the manufacturers. Samples were submitted to a 20 μl reaction using TaqMan Amplification system with an ABI PRISM 7000 Sequence Detection system (Applied Biosystems, Foster City, CA). Multiplex reactions were performed with 600 ng of cDNA for kinin B$_1$ receptor and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) amplification. Oligonucleotide primers and fluorogenic probe sets for TaqMan real-time PCR were designed for kinin B$_1$ receptor using Assays-by-Design service (Applied Biosystems) to meet all TaqMan design guidelines. The probes were synthesized with the reporter dye 6-carboxyfluorescein (6-FAM) covalently linked at the 5'-end, and the quencher dye 6-carboxy-tetramethyl-rhodamine was linked to the 3'-end of the probe. For GAPDH amplification, commercial TaqMan rodent GAPDH control reagents (Applied Biosystems) were used. Differently from kinin B$_1$ receptor probe, the GAPDH probe was VIC-labeled, allowing us to use it for multiplex detection. Each reaction was performed with 10 μl of Master Mix (Applied Biosystems), 1 μl of a mix containing two primers (18 μM each) and a probe (5 μM) specific to mRNA of kinin B$_1$ receptor (probe B$_1$: 5'-CACAGGAACCCAGACAG-3', forward primer: 5'-CCATACAAAACCCCAGCTGAA-3', reverse primer: 5'-CTTTGGTTAGAAGGCTGTAGCTTCA-3'), and 1 μl of each GAPDH primer and the VIC-labeled probe (10 μM each). The cycle conditions were as follows: 50°C for 2 min and then 95°C for 10 min, followed by 50 cycles of 95°C for 15 s (melting step), and 60°C for 1 min (anneal/extend step). Both FAM and VIC correspondent fluorescences were acquired at the end of each extend phase. The PCR cycle, when a given fluorescence threshold is crossed by the amplification curve, was considered our first parameter to analyze mRNA expression and named Ct. ΔCt values were calculated by subtracting GAPDH Ct from kinin B$_1$ receptor Ct to obtain the $2^{-\Delta Ct}$ parameter, which represents relative B$_1$ receptor/GAPDH expression.

Measurement of overt nociception. The procedure used was similar to that described previously (Ferreira et al., 2004). Twenty microliters of des-Arg^9-bradykinin solution (10 nmol/paw; Sigma) were injected intraplantarly under the surface of the right hindpaw 2 d after sham surgery or partial sciatic nerve lesion in wild-type mice. Separate groups of animals received an intraplantar injection of vehicle (PBS). Animals were placed individually in chambers (transparent glass cylinders of 20 cm diameter) and were adapted for 20 min before algogen or vehicle injection. After challenge, mice were observed individually for 10 min. The amount of time spent licking the injected paw was measured with a chronometer and was considered as indicative of overt nociception.

Skin temperature measurement. Apart from nociceptive hypersensitivity, sciatic nerve lesions may cause abnormal cutaneous temperature regulation. Thus, the skin temperature of the ipsilateral and contralateral paw was measured 7 d after surgery using a surface radiation thermometer (Pro Check, Taipei, Taiwan) as described previously (Ferreira et al., 2004).

Data analysis. The results are presented as means ± SEM of four to six animals. The statistical significance of differences between groups was
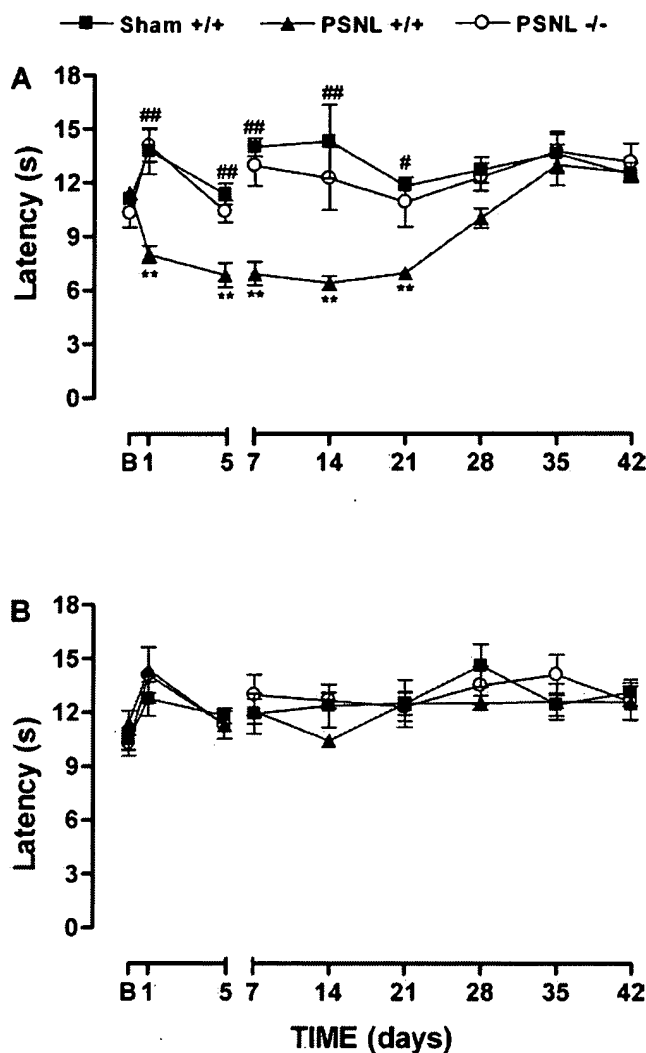
Figure 1. Time-dependent thermal hyperalgesia in the ipsilateral paw (*A*) but not in contralateral paw (*B*) induced by partial sciatic nerve lesion (PSNL) in wild-type (+/+) or B₁ receptor knock-out (−/−) mice. Data represent the latencies of the response to thermal stimuli. Each point represents the mean ± SEM of four to six mice. In some cases, the error bars are hidden within the symbols. *$p < 0.05$ or **$p < 0.01$ denotes the significance level when compared with the wild-type sham-operated group. ⁱ$p < 0.05$ or ⁱⁱ$p < 0.01$ denotes the significance level when compared with the wild-type PSNL group (one-way ANOVA followed by Student–Newman–Keuls test).

Figure 2. *A*, Mechanical sensitivity to von Frey hairs stimulation in wild-type (+/+) or B₁ receptor knock-out (KO) (−/−) mice before nerve injury. *B*, Increased mechanical sensitivity in the ipsilateral paw observed 7 d after partial sciatic nerve lesion (PSNL) in wild-type mice (+/+) but not in B₁ receptor knock-out mice (−/−). Data represent the response frequency to mechanical stimuli. Each point represents the mean ± SEM of four to six mice. In some cases, the error bars are hidden within the symbols. *$p < 0.05$ or **$p < 0.01$ denotes the significance level when compared with the wild-type sham-operated group. ⁱ$p < 0.05$ or ⁱⁱ$p < 0.01$ denotes the significance level when compared with the wild-type PSNL group (one-way ANOVA followed by Student–Newman–Keuls test).

analyzed by means of Student's *t* test or ANOVA followed by Student–Newman–Keuls test when appropriate. *p* values <0.05 were considered indicative of significance.

Results

Partial ligation of the sciatic nerve in the wild-type mouse produced a profound and prolonged decrease in thermal and mechanical nociceptive thresholds observed in the paw ipsilateral to the nerve lesion (Figs. 1, 2). Neither threshold changed in the sham-operated animals or in the paw contralateral to the lesion (Figs. 1, 2). We found a significant reduction in the paw-withdrawal latency to the heat stimulus as early as 1 d after nerve injury that was stable until 21 d compared with sham-operated wild-type animals (Fig. 1*A*). At 28 d after the nerve injury, the paw-withdrawal latencies to thermal stimulation returned to baseline values (Fig. 1*A*).

In the absence of neuropathy, we found no difference in the

paw-withdrawal responses to thermal stimulation between B₁ receptor knock-out mice and wild-type mice (10.3 ± 0.7 and 10.5 ± 0.6 s, respectively). Ablation of the gene for the B₁ receptor caused a significant reduction in thermal hyperalgesia produced by nerve injury (Fig. 1*A*). This anti-hyperalgesic response was observed from 1 to 21 d after lesion.

Before nerve injury, wild-type mice showed an increase in the frequency of responses to mechanical stimulation with von Frey hairs of higher forces (1–4 g) but little change in the responses to weaker von Frey hairs (0.07–0.6 g) (Fig. 2*A*). Moreover, B₁ receptor knock-out mice displayed a similar pattern of response to high and weak mechanical stimulation (Fig. 2*A*). Thus, von Frey hairs from 0.07 to 0.6 g were considered innocuous stimuli for both wild-type and B₁ receptor knock-out mice.

Mechanical allodynia produced by nerve injury was characterized by a pronounced and long-lasting increase in response frequency to innocuous von Frey hairs stimulation in the paw ipsilateral to the lesion (Fig. 2*B*). In contrast to thermal hyperal-

A —●— Sham +/+ —▲— Operated +/+ —○— Operated -/-

B

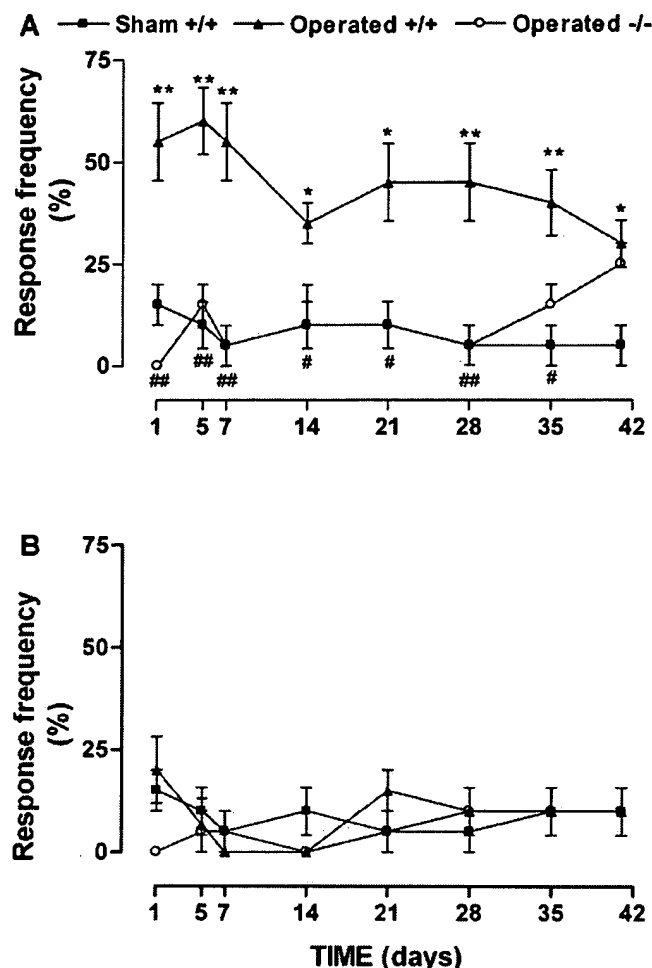**Figure 3.** Time-dependent mechanical allodynia in ipsilateral paw (A) but not in contralateral paw (B) induced by partial sciatic nerve lesion in wild-type (+/+) or B_1 receptor knock-out (−/−) mice. Data represent the frequency response to 0.16 g von Frey hair stimulation. Each point represents the mean ± SEM of four to six mice. In some cases, the error bars are hidden within the symbols. *$p < 0.05$ or **$p < 0.01$ denotes the significance level when compared with the wild-type sham-operated group. #$p < 0.05$ or ##$p < 0.01$ denotes the significance level when compared with the wild-type partial sciatic nerve lesion group (one-way ANOVA followed by Student–Newman–Keuls test).

A

Time after drug administration (h)

B

Figure 4. Antinociception produced by treatment with the selective B_1 receptor antagonist des-Arg^9-[Leu^8]-bradykinin (DALBK; 150 nmol/kg) in mechanical allodynia in the ipsilateral paw observed after partial sciatic nerve lesion in wild-type mice. A, Time course of the anti-allodynic effect 7 d after surgery. B, Anti-allodynic effect of DALBK 7–42 d after nerve injury when administered 1 h before mechanical allodynia measurement. Data represent the frequency response to 0.16 g von Frey hair (VFH) stimulation. Each point represents the mean ± SEM of five to six mice. *$p < 0.05$ or **$p < 0.01$ denotes the significance level when compared with PBS-treated mice. ##$p < 0.01$ denotes the significance level when compared with baseline (B) value without hair stimulation (one-way ANOVA followed by Student–Newman–Keuls test). The point 0 on the x-axis represents the measured mechanical allodynia immediately before drug treatment.

gesia, mechanical allodynia developed at day 1, reached a maximum at day 7 after nerve ligation, and remained increased for >42 d (Fig. 3A). B_1 receptor gene deletion completely reversed mechanical allodynia from 1 to 28 d after nerve injury (Fig. 3A). However, this anti-allodynic effect became only partial 35 d after lesion and disappeared at day 42 (Fig. 3B). Moreover, we were not able to detect mechanical allodynia in the contralateral paw (data not shown).

To further confirm the participation of the B_1 receptor in neuropathic pain, a separate group of wild-type mice was treated with the selective B_1 receptor antagonist des-Arg^9-[Leu^8]-bradykinin (150 nmol/kg, s.c.). Des-Arg^9-[Leu^8]-bradykinin administration to wild-type mice 7 d after partial sciatic nerve ligation, when the maximal pain hypersensitivity is already installed, also greatly reduced the mechanical allodynia (Fig. 4). The antinociceptive effect of des-Arg^9-[Leu^8]-bradykinin was short-lasting, maximal 1 h after treatment (inhibition of 69.6 ± 5.9%). In agreement with that after gene deletion, this dose of antagonist did not alter the frequency responses of mechanical stimulation of sham-operated animals (50 ± 5.7 and 45 ± 5.0% of frequency

responses against 2.0 g of stimulation when assessed 7 d after injury). As occurred for the gene lacking, the treatment with des-Arg^9-[Leu^8]-bradykinin was also capable of reducing mechanical allodynia when the antagonist was administered 14 and 28 d, but not 42 d, after nerve injury (Fig. 4B).

Next, the expression of B_1 receptor mRNA was quantified by real-time reverse transcription (RT)-PCR in tissues of mice after sciatic nerve lesion or sham operation. Basal expression of B_1 receptor mRNA was detected in plantar hindpaw skin, sciatic nerve, spinal cord, and cerebral cortex of wild-type mice (Fig. 5). However, 7 d after nerve lesion, we observed an increased of B_1 expression in ipsilateral paw skin, right sciatic nerve, and spinal cord obtained from operated mice (Fig. 5). No expression of B_1 receptor mRNA could be detected in B_1 receptor gene-deficient mice (results not shown). Moreover, the increase of expression of B_1 receptor mRNA was also detected in paw skin of injured wild-type mice 14, 28, and 42 d after nerve injury (441 ± 216, 241 ±

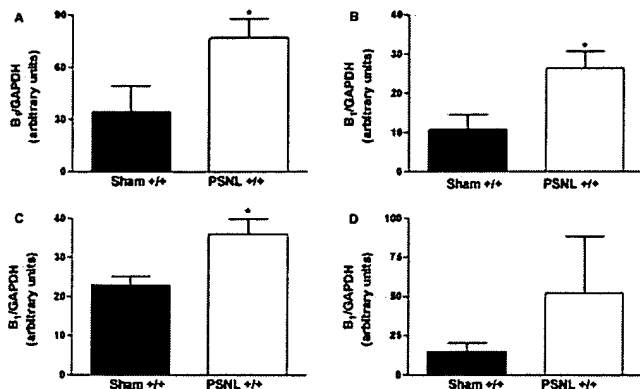**Figure 5.** Levels of expression of kinin B₁ receptor mRNA in the paw skin (A), sciatic nerve (B), spinal cord (C), and cerebral cortex (D) 7 d after sham surgery or partial sciatic nerve ligation (PSNL) in wild-type mice (+/+) assessed by real-time RT-PCR assay. All data have been normalized for levels of GAPDH expression within the same sample. Each bar represents the mean ± SEM of three to six mice. *$p < 0.05$ denotes the significance level when compared with the sham-operated group (Student's t test).

127, 849 ± 103% of increase over sham-operated animals, respectively). These results suggested that the increase in mRNA appears to mainly relate with the development and the maintenance of early stages of neuropathic pain but not with the maintenance of its late stage. In fact, intraplantar injection of the selective B₁ receptor agonist des-Arg⁹-bradykinin produced overt nociception in ligated but not in, when assessed, sham-operated wild-type mice 7 d after surgery (Fig. 6A).

In addition to nociceptive hypersensitivity, other symptoms similar to clinical features of human neuropathies may occur after partial sciatic nerve ligation in mice, including abnormal cutaneous temperature regulation. Accordingly, we observed a significant increase in the skin surface temperature of the ipsilateral paw 7 d after nerve injury in wild-type mice (Fig. 6B). Notably, the B₁ receptor gene deletion abolished this cutaneous heating (Fig. 6B). However, we were not able to detect significant modifications in skin temperature from 14 to 42 d after nerve injury either in operated or in sham-operated animals (results not shown).

Discussion

Painful neuropathies may result from nerve injury as well as the effects of drugs, diseases, toxins, and metabolic disorders (Woolf and Mannion, 1999). Because of the as yet poor understanding of the mechanisms underlying these syndromes, therapy does not provide satisfactory pain relief for many patients. Consequently, these patients suffer from chronic intractable pain (Seltzer, 1995).

Several studies have demonstrated the participation of kinins and their receptors in neuropathic pain induction. Increased levels of B₁ and B₂ receptor mRNA or protein have been found in dorsal root ganglia (DRGs) after sciatic nerve constriction in rats and mice (Petersen et al., 1998; Eckert et al., 1999; Levy and Zochodne, 2000; Yamaguchi-Sase et al., 2003; Rashid et al., 2004). Of note, the systemic administration of B₁ or B₂ receptor antagonists has been found to reduce thermal hyperalgesia and mechanical allodynia produced by sciatic nerve constriction in rats (Levy and Zochodne, 2000; Yamaguchi-Sase et al., 2003; Gougat et al., 2004). Plasma seems to be the main source of endogenous kinins after nerve injury, and there is recent evidence demonstrated that neuropathic pain is reduced in mutant plasma
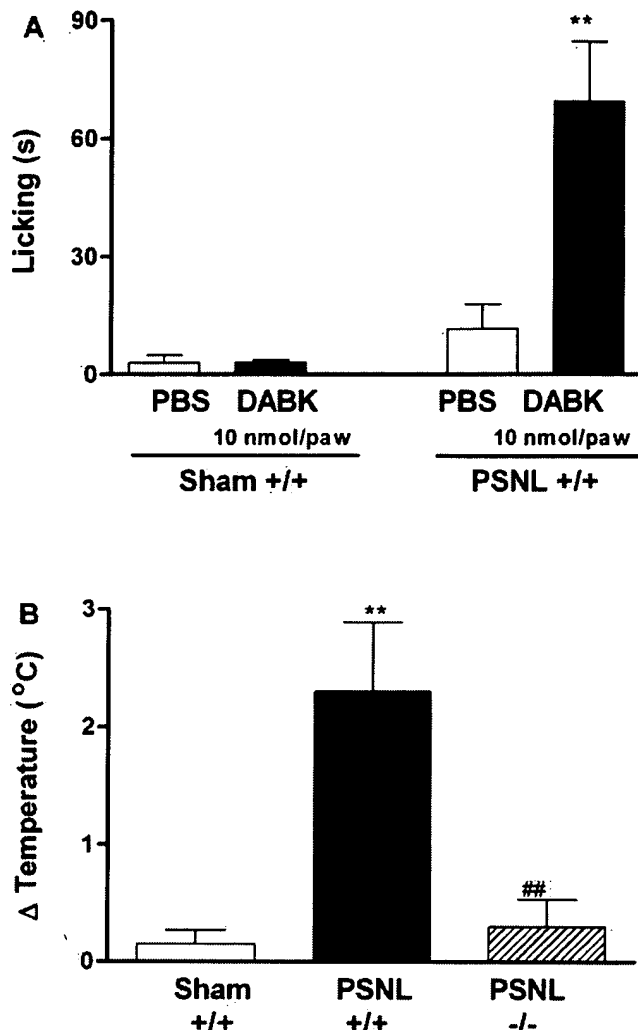
Figure 6. A, Overt nociception produced by intraplantar injection of des-Arg⁹-bradykinin (DABK; 10 nmol per paw) in wild-type mice (+/+) 7 d after partial sciatic nerve ligation (PSNL). B, Difference in temperature [Δ Temperature (°C)] between ipsilateral and contralateral hindpaw surface observed 7 d after unilateral sciatic nerve lesion. Each point represents the mean ± SEM of four to six mice. **$p < 0.01$ denotes the significance level when compared with wild-type sham-operated group. ##$p < 0.01$ denotes the significance level when compared with wild-type PSNL group (one-way ANOVA followed by Student–Newman–Keuls test).

kininogen-deficient B/N-Katholiek rats when compared with normal B/N-Kitasato rats (Yamaguchi-Sase et al., 2003).

The present work extended these previous observations by demonstrating that gene deletion or pharmacological inhibition of the B₁ receptor in mice practically abolished the nociceptive hypersensitivity produced by nerve injury. This effect appeared as early as 1 d after lesion, and it was found significant until 28 d after the surgery, suggesting that the B₁ receptor is critically involved in both the development and the early maintenance of neuropathic pain symptoms. In contrast, thermal hyperalgesia was not observed, and mechanical allodynia was reduced only in the later stages of nerve injury (35–42 d after surgery), despite the detection of increased levels of B₁ receptor mRNA. Interestingly, at this time, the mechanical allodynia was reinstalled in B₁ receptor knock-out mice, and the B₁ receptor antagonist was not capable of reducing allodynia. Because regeneration occurs after constrictive injury to the sciatic nerve (Myers et al., 1996), it is quite possible that under this circumstance, B₁ receptor activity is

not relevant to the production of neuropathic pain and probably other mediators substitute for the nociceptive action of kinins.

Pain is produced by the stimulation of small-diameter primary afferent fibers that innervate regions of the head and body and arise from cell bodies in the trigeminal ganglion and DRG, respectively (Julius and Basbaum, 2001). B_1 receptor mRNA and protein are constitutively expressed in mouse, rat, and monkey DRG (Seabrook et al., 1997; Levy and Zochodne, 2000; Ma et al., 2000; Wotherspoon and Winter, 2000; Shughrue et al., 2003; Yamaguchi-Sase et al., 2003; Rashid et al., 2004). B_1 receptors are predominantly expressed by small-diameter DRG neurons colocalized with isolectin B4 and calcitonin gene-related peptide that are contained in C and Aδ fibers (Ma, 2001). Moreover, the B_1 receptor is expressed in both peripheral and spinal terminals of primary afferent fibers (Wotherspoon and Winter, 2000; Ma and Heavens, 2001; Shughrue et al., 2003). B_1 receptors are newly expressed 7 d after partial sciatic nerve injury in mice mainly in non-neuronal satellite cells and in large myelinated DRG neurons (Rashid et al., 2004). Because there is evidence that large A fibers mediate the mechanical allodynia in rats with partial sciatic nerve lesion (Shir and Seltzer, 1990) and B_1 receptor knock-out mice have reduced allodynia, it seems that this novel expression of B_1 receptors is potentially related to the production of the persistent mechanical allodynia observed in the early stages of neuropathy.

In the present study, we have shown that B_1 receptor mRNA was normally expressed in some tissues important for the detection, transmission, and modulation of pain, including plantar paw skin, sciatic nerve, spinal cord, and cerebral cortex. Moreover, the involvement of B_1 receptors in neuropathy was further confirmed by the upregulation of B_1 receptor mRNA several days after sciatic nerve injury. It has been well demonstrated that several stimuli are able to upregulate B_1 receptor, including proinflammatory cytokines, mitogen-activated protein kinases (MAPK), and nuclear factor κB (NFκB) (for review, see Calixto et al., 2000, 2004). We can suggest that similar mechanisms might be involved in B_1 receptor upregulation in the present study, because proinflammatory cytokines are produced, and MAPK and NFκB are activated after sciatic nerve injury (Ma and Bisby, 1998; Okamoto et al., 2001; Ma and Quirion, 2002). We also observed an increase in levels of B_1 receptor mRNA in samples of ipsilateral paw skin and sciatic nerve 7 d after injury, a finding that could suggest a role for B_1 receptors in the abnormal perception of noxious and innocuous stimuli seen in early stages neuropathy. This upregulation seems to be functional, because the intraplantar injection of the selective B_1 receptor agonist des-Arg⁹-bradykinin produced overt nociception in nerve-injured, but not in sham-operated, wild-type mice. These results reinforce the recent data obtained by Rashid et al. (2004), showing that intraplantar administration of des-Arg¹⁰-kallidin was able to induce both nociceptive reflex and activation of ERK (extracellular signal-regulated kinase) in DRG neurons in ligated, but not sham-operated, mice.

B_1 receptors are also found in the CNS, which contains all of the components of the kallikrein-kinin system and is also involved in nociceptive processing (Couture and Lindsey, 2000; Ferreira et al., 2002). B_1 receptors have been identified in the superficial layers of the dorsal horn confined mainly to the terminals of primary sensory nerve fibers (Couture and Lindsey, 2000; Wotherspoon and Winter, 2000). Using an *in vitro* spinal cord preparation, Pesquero et al. (2000) demonstrated that B_1 receptor stimulation increases the C-fiber component, but not the Aβ-fiber component, of the ventral root potential produced by electrical excitation of the dorsal root of naive mice. This

indicates that the B_1 receptor functions specifically in nociceptive synaptic pathways and appears to be involved in some forms of central sensitization. In fact, intrathecal injection of B_1 receptor antagonists reduces the inflammatory phase of formalin-induced pain and chronic inflammatory pain caused by Complete Freund's Adjuvant in mice and rats (Ferreira et al., 2002; Fox et al., 2003). Moreover, the use-dependent facilitation of spinal cord neuron firing (wind-up) was significantly reduced ($\sim$50%) in B_1 receptor knock-out mice when compared with the wild-type littermates (Pesquero et al., 2000). We have shown that B_1 receptor mRNA is upregulated in dorsal spinal cord after partial sciatic nerve lesion, further suggesting a role for spinal B_1 receptors in neuropathy. Because the development of spinal sensitization is an important consequence of nerve injury (Sah et al., 2003), these data indicate that the nociceptive impairment observed in B_1 receptor knock-out mice might be attributed to, at least in part, a deficit in the pathological plasticity of the spinal neurons.

Subsets of dorsal horn neurons that project axons and transmit pain messages to higher brain structures are involved in the somatic, affective, and autonomic responses to pain (Hunt and Mantyh, 2001). In this respect, we have shown that B_1 receptor mRNA is constitutively expressed in the cerebral cortex of mice. This result is in line with literature showing basal B_1 receptor expression in rat somatosensory cortex (Ongali et al., 2003; Shughrue et al., 2003). However, the function of cortical B_1 receptors still remains obscure.

Besides thermal and mechanical hypersensitivity, animals subjected to sciatic nerve injury exhibit other signs similar to clinical features of human painful neuropathies, including abnormal sympathetic activity, abnormal growth of hair, and cutaneous temperature regulation (Wakisaka et al., 1994). Similar to our observations in mice, the ipsilateral plantar surface in rats was warmer than that of the contralateral paw during the first week after loose ligation of sciatic nerve, thereafter becoming cooler (Wakisaka et al., 1991, 1994). It has been reported that early heating of the paw surface is dependent on sympathetic vasoconstriction (Wakisaka et al., 1994). Furthermore, partial nerve injury-induced pain is mediated by sympathetic activity (Shir and Seltzer, 1991; Malmberg and Basbaum, 1998). Interestingly, functional B_1 receptors are expressed in sympathetic neurons, because their activation by agonists is able to depolarize superior cervical ganglia neurons *in vitro* (Seabrook et al., 1995, 1997). In addition, postganglionic sympathetic terminals are involved in B_1 receptor agonist-induced hyperalgesia (Khasar et al., 1995). However, the participation of sympathetic fibers in nociception mediated by B_1 receptors activation during neuropathy still needs to be determined.

Besides being caused by nerve injury, painful neuropathy may also develop in diabetes (Woolf and Mannion, 1999; Sah et al., 2003). It has been reported recently that thermal hyperalgesia in diabetic mice was blocked by the systemic treatment with selective B_1 receptor antagonists (Gabra and Sirois, 2002, 2003a,b). Moreover, intrathecal administration of a B_1 receptor agonist produces thermal hyperalgesia in hyperglycemic rats (Couture et al., 2001). Thus, the activation of B_1 receptors is a critical step in the production of neuropathic pain, and B_1 receptor blockade is able to not only prevent the development of nociception but also reduce an established painful condition. Of interest are the results showing that oral treatment with the newly synthesized nonpeptide B_1 receptor antagonist SSR240612 [(2R)-2-[((3R)-3-(1,3-benzodioxol-5-yl)-3-[[(6-methoxy-2-naphthyl)sulfonyl]amino] propanoyl)amino]-3-(4-[[2R,6S)-2,6-dimethylpiperidinyl]methyl]

phenyl)-N-isopropyl-N-methylpropanamide hydrochloride] was able to reduce the thermal hyperalgesia produced by sciatic nerve injury in rats (Gougat et al., 2004). These findings support the notion that the development of oral-selective B_1 receptor antagonists might be expected to have clinical therapeutic potential in the management of neuropathic pain.

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The Assessment of the Patient with **Pain**

I. OVERVIEW

A. Core questions to be answered as part of a pain assessment:

· What is the type or category of **pain**?

· Is there a primary cause of the **pain**?

· What additional factors are contributing to the **pain**?

· Are treatments available for the primary cause of the **pain**?

· Are treatments available for the additional factors which contribute to the **pain**?

· Are there other medical or psychosocial conditions which should influence the choice of treatment?

B. The methodology of the pain assessment:

· History

· Past medical history

· Current medications

· Physical examination

· Special tests

· Psychological evaluation

· Differential diagnosis

II. INTRODUCTION

The basics of the assessment of **pain** are the same as the assessment of other medical complaints. Yet **pain** is the most common complaint that presents to the primary care practitioner; therefore, it is valuable to give some focused attention to the specifics of the methodology for assessing this problem.

III. CORE QUESTIONS TO BE ANSWERED AS PART OF A PAIN ASSESSMENT

A. *What is the type or category of pain? 8*

1. Nociceptive Pain --

This is the typical **pain** that we have all experienced. It is the signal of tissue irritation, impending injury, or actual injury. Nociceptors in the affected area are activated and then transmit signals via the peripheral nerves and the spinal cord to the brain. Complex spinal reflexes (withdrawal) may be activated, followed by perception, cognitive and affective responses, and possibly voluntary action. The **pain** is typically perceived as related to the specific stimulus (hot, sharp, etc.) or with an aching or throbbing quality. Visceral **pain** is a subtype of nociceptive **pain**. It tends to be paroxysmal and poorly localized, as opposed to **somatic pain** which is more constant and well localized. Nociceptive **pain** is usually time limited--arthritis is a notable exception--and tends to respond well to treatment with opioids.

2. Neuropathic Pain --

Neuropathic pain is the result of a malfunction somewhere in the nervous system. The site of the nervous system injury or malfunction can be either in the peripheral or in the central nervous system. The **pain** is often triggered by an injury, but this injury may not clearly involve the nervous system, and the **pain** may persist for months or years beyond the apparent healing of any damaged tissues. In this setting, **pain** signals no longer represent ongoing or impending injury. The **pain** frequently has burning, lancinating, or electric shock qualities. Persistent allodynia--**pain** resulting from a nonpainful stimulus, such as light touch--is also a common characteristic of **neuropathic pain**. **Neuropathic**

pain is frequently chronic, and tends to have a less robust response to treatment with opioids.

<table>
<tr><td>

Categories of Pain

— Nociceptive
- Somatic
  - constant, aching, gnawing, throbbing, well localized
- Visceral
  - paroxysmal, deep, aching, squeezing, poorly localized

— Neuropathic
- burning, lacinating, electric
- follows nervous system injury or malfunction
- central
  - may result from chronic pain & persist after healing
- peripheral

</td><td>

Neuropathic Pain Problems
- Postherpetic Neuralgia
- Reflex Sympathetic Dystrophy / Causalgia
- Cancer Pain Components
- Phantom Limb Pain
- Neuroma
- Trigeminal Neuralgia
- Entrapment Neuropathy
- Peripheral Neuropathy
  - diabetic, alcoholic
- Myelopathy -- post-traumatic, HIV

</td></tr>
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3. Psychogenic Pain--

The use of this category should be reserved for those rare situations where it is clear that no **somatic** disorder is present. It is universal that psychological factors play a role in the perception and complaint of **pain**. These psychological factors may lead to an exaggerated or histrionic presentation of the **pain** problem, but even in these circumstances, it is rare that the psychological factors represent the exclusive etiology of the patient's **pain**.

4. Mixed Category Pain--

In some conditions the **pain** appears to be caused by a complex mixture of nociceptive and **neuropathic** factors. An initial nervous system dysfunction or injury may trigger the neural release of inflammatory mediators and subsequent neurogenic inflammation. For example, migraine headaches probably represent a mixture of **neuropathic** and nociceptive **pain**. Myofascial **pain** is probably secondary to nociceptive input from the muscles, but the abnormal muscle activity may be the result of **neuropathic** conditions. Chronic **pain**, including chronic myofascial **pain**, may cause the development of ongoing representations of **pain** within the central nervous system which are independent of signals from the periphery. This is called the centralization or encephalization of **pain**.

B. Is there a primary cause of the pain?

After determining if the **pain** is most likely nociceptive or **neuropathic**, the next step is to determine, as precisely as possible, the cause or specific source of the **pain**. Frequently, reversible causes can be identified. Nociceptive **pain** indicates ongoing or impending injury; therefore, identification and removal or treatment of the problem is critical. Is there an underlying sprain, tear, fracture, infection, obstruction, or foreign body? Is there inflammation caused by an underlying arthritic or autoimmune disorder? Myofascial **pain** may indicate abnormal acute or chronic muscle stresses. **Neuropathic pain** may also be caused by injury, but the injury in that case is actually to the nervous system. Nerves can be infiltrated or compressed by tumors, strangulated by scar tissue, or inflamed by infection. Some of these, and other **neuropathic** etiologies, may also be reversible.

Usually, **neuropathic** problems are not fully reversible, but partial improvement is often possible with proper treatment. For example, neuromas may respond to excision or ablation; phantom **pain** may respond to transcutaneous nerve stimulation (TENS); and peripheral neuropathy may respond to tricyclic antidepressants.

C. What additional factors are contributing to the pain?

For most of the last 300 years, our understanding of **pain** has been dominated by the Cartesian model. Viewed from this perspective, the human body is a complex machine which is separate and distinct from the mind and the process of perception. Therefore, physical **pain** is a function of the mechanics of the body. In the last 30 years, we have come to appreciate that **pain** is an experience rather than a bodily function. Experience is a function of the mind; therefore, the experience of **pain** cannot be separated from the patient's mental state, including their social-cultural background. We now know that environmental and mental factors can be so critical that they can actually trigger or abolish the experience of **pain**, independent of what is occurring in the body.[38] We now understand some of the mechanisms of how the brain can influence the spinal processing of **pain** via descending inhibitory and facilitory neural pathways. Furthermore, suffering should not be considered synonymous with **pain**. The emotional impact and distress caused by **pain differs** from person to person. Different patients may report very different intensities of **pain** for similar injuries, but even when they report similar degrees of **pain**, they may have vastly different amounts of suffering.

When assessing a complaint of **pain**, it is critical to remember that **pain** is an experience, rather than a bodily function. Therefore it is valuable to investigate the appropriate mental and environmental factors:

1. Mood disorder--

Depressive disorders are found in approximately 50% of chronic **pain** patients. [33] The patient may say, "Cure the **pain**, and I won't be depressed;" however, it would be a mistake to ignore the depression. Depression can significantly intensify the experience of **pain** and the associated suffering. In some cases, depression manifests primarily with **somatic** symptoms and complaints. Therefore, on occasion, depression may even be the primary etiology of the **pain**.

2. Anxiety disorder--

Again, more than 50% of chronic **pain** patients suffer with anxiety disorders which may alter the experience of **pain** and suffering. [14]

3. Somatization and hypochondriasis[34]--

Stress affects the bodily functions and sensations in all people. Emotional distress is often felt and expressed as physical distress. These processes, when predominant, lead to excessive **somatic** attention and communication in the forms of somatization and hypochondriasis. These can sometimes be primary psychiatric disorders or tendencies, but often they are part of depressive or anxiety disorders. These patients are prone to misinterpreting normal bodily sensations and to exaggerating the symptoms of illness. They are therefore more likely to believe that they are suffering from a catastrophic illness

or complication.

4. Secondary gain[15]--

Patients with chronic **pain** undergo many losses--financial, vocational, recreational, and impaired relationships. They also incur benefits which may be financial or involve emotional support from friends and family. If the secondary gains outweigh the secondary losses, then there may be motivational factors impeding the recovery. These factors are frequently unconscious, and they are not usually the "cause" of the **pain**. Malingering occurs in those rare situations where the patient is consciously lying about their condition for reasons of gain. Also rarely, the patient may be consciously lying about symptoms, but without conscious benefit or gain--this represents a factitious disorder.

5. Other physical factors

· Other physical factors may also contribute to the experience of **pain**, including:

· sleep disturbance

· inactivity and poor muscle conditioning

· weight gain

· other injuries or illnesses
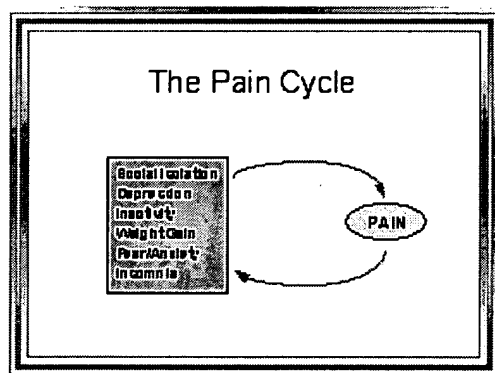
D. Are treatments available for the primary cause of the pain? 28,36

The physician will find it valuable to have some familiarity with the treatments available for various **pain** syndromes. Subsequent chapters in this handbook will help to find information regarding available therapies.

Nociceptive **pain** is usually quite responsive to treatment with classical analgesics such as narcotics, nonsteroidal antiinflammatory drugs, or acetaminophen. Frequently, synergistic effects can be achieved by combining these medications. For acute, nociceptive **pain**, regional or nerve block techniques may also be effective. Clearly, while analgesia is being provided, the clinician must be diligently searching for underlying sources of tissue injury, irritation, or inflammation. TENS (transcutaneous electrical nerve stimulation) units and relaxation training may also benefit the patient suffering with nociceptive **pain**.

Neuropathic pain also typically responds to treatment with narcotics, but less robustly than does nociceptive **pain**. Anticonvulsants and tricyclic antidepressants may be particularly beneficial. The allodynia (**pain** in response to a non-noxious stimulus) and hyperalgesia present in some **neuropathic** conditions may, in part, be the result of the production of increased numbers of adrenergic receptors on sensory nerve terminals and on surrounding inflammatory and mast cells. Therefore, sympatholytics such as clonidine, prazosin, and terazosin may be helpful in decreasing allodynia and hyperalgesia. Antiarrhythmics, most notably mexiletine, may alter neuronal sodium channel conduction, and thereby decrease ectopic or abnormal firing with in damaged, malfunctioning, **pain** producing parts of the nervous system. Referral to a **Pain** Clinic may be helpful in guiding further treatment or complex pharmacotherapy for the patient with chronic **neuropathic pain**. Other treatments might include nerve blocks, TENS units, biofeedback, psychological and physical therapies.

Pharmacology & Neuropathic Pain

Tricyclic antidepressants

Anticonvulsants

Antiarrhythmics

Sympatholytics

E. Are treatments available for the additional factors which contribute to the pain?

For **pain** treatments to be fully effective it is critical that all factors be treated simultaneously. If depression or anxiety are contributing, these are highly treatable conditions. Appropriate therapy with antidepressants or anxiolytics, together with psychotherapy, should be instituted early in the treatment process.

Somatization and hypochondriasis are more chronic and relatively more refractory conditions. However, here too, psychotherapeutic and possibly psychopharmacologic interventions may be critically helpful components of the treatment for the chronic **pain** patient. An understanding of these factors will also help to guide all aspects of the patients treatment. For example, the patient who is prone to high levels of somatization, is a relatively poor candidate for invasive treatments, since such interventions are likely to exacerbate the patients **somatic** concerns and preoccupation. [31]

Secondary gain is not an illness, nor is it treated, but we must pay attention to this factor. The physician must be careful not to alter the balance of secondary losses versus secondary gains in such a manner that tips the scales in the direction of greater illness and disability. Psychotherapy may also help the patient to recognize that disability is associated with greater losses and fewer gains than the patient might consciously or unconsciously realize. Factitious disorders, when identified, indicate that treatment must focus on intensive psychotherapy (although it is difficult to get the patient to be compliant

with such treatment). Malingering is a moral and legal problem rather than a medical problem, but recognition of malingering can help to avoid unnecessary, costly, and potentially dangerous treatments. [15, 31]

Other health factors, such as sleep, weight, and overall conditioning can also contribute to the problem. Like most of the above associated factors, **pain** can cause these problems and then, in a vicious cycle, be exacerbated by these same problems. Appropriate medical management focused on these problems can be most beneficial.

F. Are there other medical or psychosocial conditions which should influence the choice of treatment? [31]

The previous questions have focused on understanding the nature of the patient's **pain** and the additional factors contributing to the problem. When treating the patient it is important to consider what other conditions or factors (which are not directly contributory to the **pain**) might influence the choice of treatment.

Other medical conditions, such cardiac or pulmonary disease, may be relative contraindications for some medications or for various blocks. Examples include arrhythmias (especially bundle branch blocks) as a relative contraindication for tricyclic antidepressants or for right stellate ganglion blocks, bullous emphysema as a contraindication for intercostal nerve blocks, and pulmonary disease in general as a cautionary note regarding the use of narcotics (especially intravenous narcotics).

Psychiatric conditions may also influence the choice of treatment. A history of mania or bipolar disorder is a relative contraindication for the use of antidepressants, a history of recent drug abuse indicates a need to avoid narcotics or benzodiazepines where possible, and high levels of somatization or anxiety argue against the use of invasive techniques or therapies.

Some of the newer and more invasive **pain** therapies, such as spinal dorsal column stimulators and intrathecal morphine pumps, require that the patient have a good understanding of the medical condition and be highly compliant with complex treatments.

IV. THE METHODOLOGY OF THE PAIN ASSESSMENT

The previous section reviewed the overall questions that the care provider should keep in mind when assessing a complaint of **pain**. The next section provides some of the specifics of the data gathering process.

A. History [6, 12]

Critical Elements of the Pain History

A. How the pain developed
B. The description of the pain
C. The location of the pain and any spread
D. The pattern of the pain over time
E. The patient's level of function and impairment
F. The previously attempted treatments

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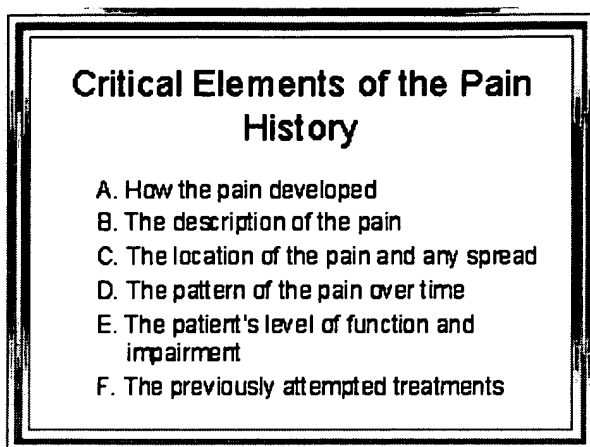
1. How the pain developed?

Was there an injury, illness, or major stress associated with the start of the **pain**?

This may give clues regarding any underlying pathology.

Did the **pain** start immediately after the injury or was there a delay of weeks or months?

Neuropathic pains such as entrapment neuropathy or complex regional **pain** syndromes (RSD) frequently development weeks to months after the injury.

Is the **pain** associated with any treatment or medication?

Headaches may occur as a rebound phenomena, associated with the use of analgesics. Occasionally, physically manipulative therapies may exacerbate a painful condition.

Has the condition been stable or deteriorating?

Ongoing deterioration mandates a more aggressive search for underlying pathology and possible interventions. Worsening low back **pain**, especially with deteriorating neurologic signs, may require surgical intervention; as opposed to stable, chronic low back **pain**, where more conservative measures are usually more appropriate.

2. Description of the pain.

What are the adjectives used to describe the **pain**?

The patient's description of the **pain** can help determine the type of **pain**. See the previous section on categories of **pain**. The patient's choice of adjectives may also provide clues regarding the emotional impact of the **pain**.

Are there associated symptoms, such as nausea or sweating, flushing, or sensations of hot or cold in the affected area?

These symptoms may indicate a autonomic or sympathetic component of the **pain**.

How intense is the **pain**?

There is tremendous individual variation in the perception of the intensity of **pain**. Yet obtaining this information is very important to help gauge the impact of the **pain**, and for the monitoring of change or progress.

Standardizing the **pain** description.

The Visual (or Verbal) Analog Scale (VAS) is the most common method for assessing **pain** intensity, and its change over time.

No pain   Worst possible **pain**

The patient is presented with a 10 cm line, labeled as above, and asked to mark an `X' on the line indicating the intensity of their **pain**. The result is then measured with a metric ruler and scored between 0 - 10. The same scale can be given verbally by asking the patient, "On a scale of 0 to 10, with 0 meaning no **pain**, and 10 meaning the worst **pain** you can imagine, how much **pain** are you having now?" These scales can also be used to assess the range of the patient's **pain** by asking them to indicate their level of **pain** at its worst, its best, and its average.

Similar scales are available for children. The FACES scale shows cartoon-like pictures of faces in various degrees of distress. The child is asked to choose the one that shows how much **pain** she is having.

Standardized, multiple choice lists of **pain** adjectives are also useful, especially in a **pain** clinic setting. The McGill **Pain** Inventory is the most commonly used of these. It may also be useful to ask the patient to keep a diary of their **pain** problem. The downside to this approach is that it asks to the patient to maintain a focus on their **pain**; this may be counterproductive to their treatment.

3. The location of the pain and any spread.

Pain drawings.

Ask the patient to draw the distribution of their **pain** on an outline of the human body.

Is the **pain** limited to the distribution of a root or peripheral nerve?

Such distributions help to isolate the site and possibly the source of the pathology. **Pain** which does not have a limited distribution, but instead occurs in multiple sites or has a diffuse distribution, implies a systemic etiology.

Is the **pain** in a stocking or glove distribution?

A stocking or glove distribution does NOT indicate a psychogenic etiology. Such a distribution is entirely consistent with a Complex Regional **Pain** Syndrome (RSD or causalgia), or if bilateral with a peripheral neuropathy.

Could the **pain** be referred from another site?

Possibly because of the convergent structure of the nervous system, it is common for **pain** to be referred from a separate, possibly quite distant site. This is most commonly seen if the site of painful stimulation or irritation is visceral or muscular. [7]

Common Examples of Referred Pain

Origin of Pain	Referred to:
Pharynx	Ear
Heart	Left shoulder, arm
Esophagus	Substernal
Diaphragm	Shoulder
Pancreas	Mid-back
Bladder, Urethra	Perineum, penis

4. How does the pain fluctuate over time.

Is there any daily, monthly, or seasonal pattern associated with the **pain**?

The physician is looking for clues as to the etiology of the **pain**. Arthritic conditions may be worse in the mornings and during cold seasons. Migraine headaches may have occur in patterns associated with a variety of factors such as stress or menstrual cycling.

Are there aggravating or alleviating factors which lead to exacerbation or reduction of the **pain**?

Understanding aggravating and alleviating activities can help to pinpoint the diagnosis or refine the treatment. Low back **pain** which is worse walking uphill suggests a discogenic etiology. If the **pain** is worse when walking downhill, this points more to facet disease or foraminal stenosis. Some headache syndromes are triggered by specific dietary elements such as alcohol or monosodium glutamate (MSG). Identifying and avoiding these triggers can be most helpful.

5. What is the overall level of patient function?

Are there changes in the patients weight and sleep pattern?

Such changes suggest the need to investigate further regarding possible depression or cancer.

What is the patient's employment status?

Issues of lost productivity and income or workers compensation may affect the patient's emotional and motivational state. It is usually a priority to enable the patient to return to work as soon as possible--vocational rehabilitation may be a crucial part of the treatment.

What are the patient's daily activities?

Understanding the day-to-day activities of the patient and what activities are limited by the **pain** will help the clinician to focus the physical and psychological rehabilitation process. If the patient has acquired a totally disabled lifestyle, then it may be important to help the patient understand that he is capable of some productive functioning.

Is the patient engaging in any exercise and physical activity?

Physical activity is critical for preventing further physical deterioration. Exercise is often a crucial part of the treatment process; however, it is important that the patient's physical activities be reviewed, since some activities may exacerbate the problem.

What is the quality of the family and personal relationships?

Chronic **pain** may lead to irritability and personality changes. Such changes may in turn lead to the deterioration of personal relationships. Such problems should be identified so that interventions can be initiated. Families typically need some education regarding adaptive responses to chronic **pain**. Overly solicitous responses may reinforce the patient's **pain** behaviors and undermine the relationship.

6. What treatments have been attempted?

Identifying prior treatment failures will not only prevent unnecessary repetition, but can also help guide the diagnosis. For example, if a variety of sympathetic blocks have not, even briefly, alleviated the **pain**, then perhaps the **pain** is not sympathetically mediated.

B. Past Medical History

In the assessment of the patient with **pain**, the past medical history should include the following information:

1. Do other medical problems relate to the patient's complaint of pain?

For example, a history of diabetes or alcoholism point towards diagnoses of neuropathy. For headaches or abdominal **pain**, have there been any recent medication changes associated with the onset of the problem.

2. Do other medical problems potentially affect the choice of pain treatments?

As noted above, the patient's medical condition may present relative contraindications to various medications or procedures.

3. Does the patient have any prior or current substance abuse history?

Treating chronic **pain** with narcotics requires special caution with the addiction prone patient. In some patients it may not be possible to use narcotics except in the most dire circumstances.

C. Current Medications

1. Dosage and pattern of use

Obtain a complete list of the patient's medications and usage. Include over-the-counter medications.

2. Effectiveness

Note the effectiveness of medications. Analgesics (even if only partially effective) should lead to some increase of function in at least one sphere of the patient's life.

3. Drug tolerance

The chronic use of some drugs is associated with tolerance (the gradual need to increase the dose to maintain the same effect). Tolerance does not imply addiction, but the development of physiologic tolerance can be hard to distinguish from inappropriate drug seeking behavior.

Drugs Associated with Tolerance

– Opiates
– Benzodiazepines
– Barbituates
– Stimulants
– rarely: local anesthetics
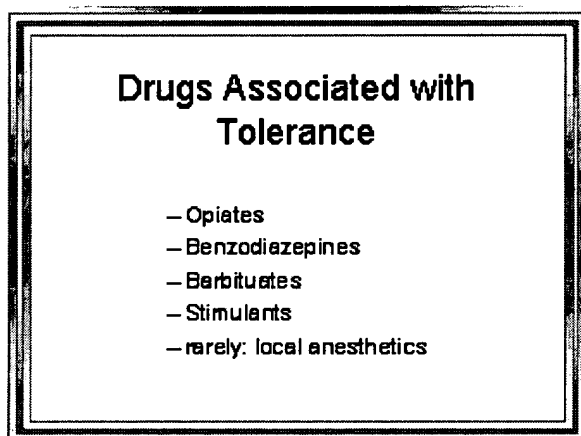
4. Potential for drug interactions and toxicity

Acetaminophen [13]

The analgesic ceiling for a single oral dose is reached at 1000 mg. There is the potential for hepatic toxicity; therefore, the daily use should not exceed 4 grams, and extra caution is warranted if the patient is malnourished or abuses alcohol.

Nonsteroidal Antiinflammatory Drugs (NSAIDs) [22, 25]

Prostaglandins are important factors in the maintenance of renal perfusion in those patients with hypovolemia or reduced renal blood flow. These patients and the elderly are at increased risk for renal damage from NSAIDs. Prostaglandins help maintain gastric mucosal integrity; therefore, NSAIDs may also produce gastroduodenal damage. All NSAIDs may provoke asthmatic reactions in patients with underlying asthma or sensitivity to aspirin or other NSAIDs. These drugs inhibit platelet function and are associated with increased bruising; they should be discontinued before surgery or other invasive procedures. NSAIDs are relatively contraindicated in patients treated with anticoagulants. There is increased risk of gastrointestinal bleeding and coumadin levels may be altered secondary to displacement from protein binding sites.

Tricyclic Antidepressants [9, 16]

The side effects and toxicity of tricyclics can be exacerbated secondary to drug interactions. Tricyclic levels are increased by the selective serotonin reuptake inhibitors, especially fluoxetine and paroxetine. Neuroleptics, cimetidine, methylphenidate, and estrogens may also increase tricyclic levels. Additive side effects may occur with alcohol, sedatives, or other anticholinergic medications. Potentially fatal interactions may occur if tricyclics are given to patients on monoamine oxidase inhibitors (MAOIs). Hypertension and hyperpyrexia may occur secondary to administration with sympathomimetics.

Tricyclic Antidepressant Side Effects

- Anticholinergic
  - mucosal dryness
  - constipation
  - urinary retention
  - confusion
  - blurred vision
  - aggravation of narrow angle glaucoma
- Anti-alpha-adrenergic
  - orthostatic hypotension
- Antihistaminic
  - sedation
- Quinidine-like
  - cardiac arrhythmias and block

Anticonvulsants [1, 16]

Carbamazepine has a similar structure to tricyclic antidepressants, it may weakly potentiate tricyclic side effects and have there is a risk of interactions with MAOIs. Disulfiram and isoniazid may increase phenytoin levels. Phenytoin may displace coumarin from protein binding sites, and may alter digoxin levels. Propoxyphene may increase carbamazepine levels. Check for altered levels of other antidepressants.

Anticonvulsant Side Effects

- Carbamazepine
  - sedation
  - headache
  - nausea & vomiting
  - leukopnea
  - thrombocytopenia
  - agranulocytosis
  - aplastic anemia
  - hepatotoxicity
  - Stevens-Johnson syndrome
- Clonazepam
  - sedation
  - cognitive impairment
  - ataxia
- Gabapentin
  - sedation
  - dizziness
  - ataxia
  - nystagmus
- Phenytoin
  - ash
  - nystagmus, diplopia
  - drowsiness
  - ataxia
  - hepatotoxicity
  - gingival hyperplasia
  - blisters
  - facial coarsening
- Valproate
  - drowsiness
  - nausea
  - weight gain
  - tremor
  - menstrual disturbance
  - thrombocytopenia
  - hepatotoxicity
  - pancreatitis
  - interstitial nephritis

Opioids [31, 32]

Opioid side effects can vary from one narcotic drug to another in an unpredictable manner for each individual. Meperidine, at doses greater than 1 gram per day, is associated with the additional risk of seizures. Meperidine combined with monoamine oxidase inhibitors (MAOIs) can trigger a fatal hyperpyrexic reaction. Opioid side effects may be enhanced by alcohol or sedatives. Propoxyphene may also cause seizures, overdose may also cause fatal heart block; furthermore, propoxyphene may increase carbamazepine levels.

Sudden discontinuation of opioids is associated with influenza-like symptoms of withdrawal:

· restlessness & insomnia

· nausea & vomiting

· diarrhea

· backache

· leg **pain**

· yawning

· lacrimation

· rhinorrhea

· mydriasis

· muscle cramps

If it is necessary to withdraw a patient from an opioid medication, it is best to decrease the dose by approximately 10% every 24 to 72 hours--further individual tailoring may be necessary.

Side Effects of Opioids

- Respiratory depression
- Nausea, vomiting
- Urinary retention
- Mental clouding
- Tolerance & dependence
- Ileus

- Sedation**
- Cough suppression**
- Constipation**
- Euphoria**
- Pruritis
- Biliary spasm

** These effects are occasionally desirable.
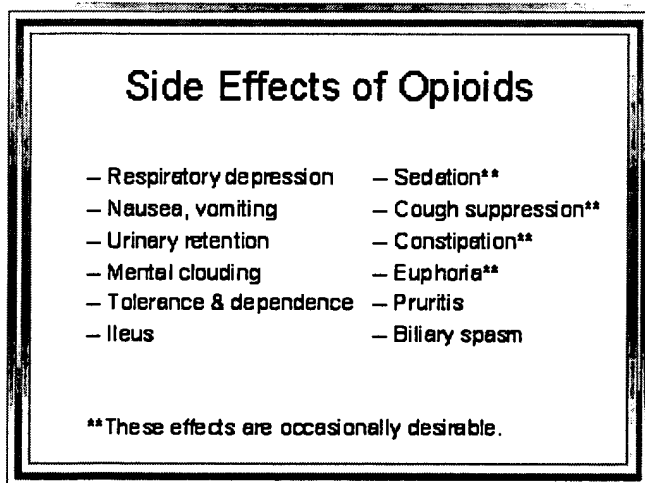
D. Physical Examination [6, 12]

Introduction

In **pain** assessments, there are rarely tests available that will "make the diagnosis." Instead the clinician must rely upon the presenting signs and symptoms. The history will often generate a differential diagnosis; the physical exam will often lead to the selection of the primary diagnosis, and occasionally a test will help to confirm this diagnosis. For example, an MRI scan which reveals an L5-S1 disc herniation is only helpful as far as it confirms or contradicts the findings of the history and physical examination.

When preparing to do a physical examination it is important to warn the patient as you approach potentially painful areas. It is also good policy to use chaperones whenever examining patients of the opposite sex.

1. Mental status exam

cognitive functions--impairment implies the presence of delirium or dementia

mood and affect--provide clues regarding the emotional state of the patient and the presence of anxiety or depression

thought process & content--check if the patient is having suicidal ideation, or if there are signs of thought disorder and possible psychosis

judgment and insight--many treatments, such as the prescribing of narcotics or the use of relaxation training, require intact judgment and insight

2. Vital signs

Vital signs are often elevated in acute **pain**.

3. Inspection

posture, guarding, splinting--if chronic, these behaviors may compound and exacerbate the **pain** problem, as the patient places abnormal stresses on the body.

color and pigmentary changes--these skin changes may indicate sympathetic dysfunction, inflammation, or a prior herpes zoster eruption.

sweating--abnormal or asymmetric sweating indicates sympathetic dysfunction.

piloerection, gooseflesh (cutis anserina)--areas involved in **neuropathic pain** may briefly demonstrate this after disrobing.

hair, nail changes--evidence of **neuropathic** injury or sympathetic dysfunction.

swelling, edema--indications inflammation or sympathetic dysfunction.

atrophy--may indicate guarding and lack of use, or denervation.

poor healing--indicates poor perfusion possibly associated with ischemic injuries, diabetic

neuropathy, or sympathetic dysfunction.

4. alpation & Musculoskeletal exam

temperature changes--indicates inflammation or altered perfusion associated with sympathetic dysfunction.

edema--subtle, subcutaneous edema can be appreciated by wrinkling the skin over affected and unaffected areas. Affected areas will not wrinkle into fine lines, but will look more dimpled, like orange peels. This indicates neural injury with denervation or sympathetic dysfunction.

muscle tenderness--examination of muscles may reveal tender areas or actual trigger points. The extent of the tenderness and the amount of pressure required to elicit **pain** should be observed. Reproduction of the patient's characteristic **pain** is particularly noteworthy.

joints--can be examined for effusions, ROM, and **pain** with compression or distraction

5. Neurologic

Cranial nerve assessment--is especially crucial in the evaluation of head and neck **pain**.

Physical examination for radiculopathy [20, 30]

UPPER EXTREMITIES

C5	Motor	raised elbows (axillary n.)
	Reflex	biceps (musculocutaneous n.)
	Sensory	upper, lateral arm, near/over deltoid (axillary n.)
	Pain	upper, lateral arm, never below elbow
C6	Motor	elbow supination (radial n.) / pronation (median n.)
	Reflex	brachioradialis (radial n.)
	Sensory	lateral forearm (musculocutaneous n.)
	Pain	lower lateral arm, possibly into thumb
C7	Motor	elbow extension (radial n.)

	Reflex	triceps (radial n.)
	Sensory	over triceps, mid-forearm, and middle finger
	Pain	deep **pain** in triceps, front and back of forearm & into middle finger
C8	Motor	thumb index pinch (ant. interosseus n. off median n. at the elbow)
	Reflex	
	Sensory	medial forearm (antebrachial cutaneous n.)
	Pain	medial forearm, into the 2 medial fingers
T1	Motor	finger abduction (ulnar n.)
	Reflex	
	Sensory	medial arm (brachial cutaneous n.)
	Pain	deep **pain** in axilla & shoulder w/ some radiation down inside of arm

Cervical spondylosis or disc protrusion can produce cord compression (upper motor neuron signs) or root compression (lower motor neuron signs). C5-6 disc protrusions are the most common cervical disc problems; they can compress the C6 root and also produce C7 upper motor signs.

Special Tests:

- 1) Cervical distraction – relieves pain
- 2) Cervical compression – provokes radicular pain from the foraminal stenosis
- 3) Valsalva -- provokes pain, especially from central cervical canal stenosis
- 4) Swallowing -- provokes pain, especially from anterior cervical spine lesions
- 5) Adson – diminished radial pulse w/ abduction, extension, external rotation of arm + head turned towards arm suggests thoracic outlet syndrome

LOWER EXTREMITIES:

L2	Motor	hip flexion (femoral n.)
	Reflex	
	Sensory	often no loss, anterior midthigh (femoral n, & lat. femoral cut br.)
	Pain	across thigh
L3	Motor	knee extension (femoral n.), thigh adduction (obturator n.)
	Reflex	hip adductors (obturator n.)
	Sensory	often no loss, anterior thigh just above the knee cap
	Pain	across thigh
L4	Motor	inversion of the foot (tibial & peroneal n.)
	Reflex	knee jerk (femoral n.)
	Sensory	medial lower leg
	Pain	across knee & down to medial malleolus
L5	Motor	dorsiflex great toe (deep peroneal n.)
	Reflex	
	Sensory	especially dorsum of the foot (peroneal n.)
	Pain	back of thigh to lateral lower leg, dorsum & sole of foot, esp. big toe
S1	Motor	eversion of the foot (peroneal n.)
	Reflex	ankle jerk (tibial n.)
	Sensory	behind the lateral malleolus
	Pain	back of thigh and calf to lateral foot

It is important to note that lumbar disc lesions can only cause root (lower motor neuron) syndromes. Hyperreflexia is a sign of disease or injury at a higher level, in the spinal cord or brain. 95% of lumbar disc lesions involve L5 or S1.

Special Tests:

- 1) Straight leg raising -- provokes radicular pain, lower slightly and dorsiflex the foot to again reproduce the pain
- 2) Crossed leg raising--raising the "good" leg provokes radicular pain in the "bad" leg
- 3) Kernig -- flex head to stretch the spinal cord and provoke root irritation pain
- 4) Milgram -- bilateral straight leg raising x2 inches, x30 seconds, or Valsalva -- provokes root irritation pain
- 5) Pelvic compression -- provokes SI joint pain
- 6) Gaenslen's sign -- knee flexed, lower other leg/buttock off edge of table, provokes SI pain
- 7) Patrick or Fabere -- fully flex, abduct, and externally rotate the hip, provokes hip or SI pain
- 8) Homans' sign -- dorsiflex foot of extended leg & deeply palpate calf for thrombophlebitic pain

Gait

Observation of gait can help identify weakness or **pain** (antalgic gait). Distortion of the patient's gait may also lead to improper muscle use and strain, leading to further **pain**.

Sensory dysfunction

Neuropathic pain is associated with nerve injury or dysfunction. Frequently, it is possible to demonstrate sensory impairment in one or more modalities including temperature, light touch, sharp/dull discrimination, position, and vibration. The examiner should test the involved areas for at least one function of large fibers, such as vibration or light touch, and one small fiber function, such as temperature (using and ice cube or alcohol swab) or sharp/dull discrimination. The examination should also make note of the presence and distribution of abnormal **pain** responses.

Table of Terms [26]

Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage.
Allodynia	**Pain** due to a stimulus which does not normally provoke **pain**.
Analgesia	Absence of **pain** in response to stimulation which would normally be painful.

Anesthesia dolorosa	**Pain** in an area or region which is anesthetic.
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked.
Hyperalgesia	An increased response to a stimulus which is normally painful.
Hyperesthesia	Increased sensitivity to stimulation, excluding the special senses.
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.
Hypoalgesia	Diminished **pain** in response to a normally painful stimulus.
Hypesthesia = Hypoesthesia	Decreased sensitivity to stimulation, excluding the special senses.
Noxious stimulus	A stimulus which is damaging to normal tissues.
Paresthesia	An abnormal sensation, whether spontaneous or evoked.

Peripheral Nerve & Dermatome Map

From DeGowin EL, DeGowin RL: Bedside Diagnostic Examination, 3rd edition, Macmillan Publishing, New York, 1976, p.809-10.

Motor dysfunction--Assessment of motor strength can help identify neural injury and the roots or peripheral nerves involved.

Grading of Muscle Strength

Grade 0	0%	Zero	No evidence of contractility
Grade 1	10%	Trace	Slight contractility but no joint motion
Grade 2	25%	Poor	Complete motion but with gravity eliminated
Grade 3	50%	Fair	Barely complete motion against gravity

| Grade 4 | 75% | Good | Complete motion against gravity and some resistance |
| Grade 5 | 100% | Normal | Complete motion against gravity and full resistance |

DeGowin EL, DeGowin RL: Bedside Diagnostic Examination, 3rd edition, Macmillan Publishing, New York, 1976, p. 768.

Abnormal Reflexes [39]

Hyporeflexia

--focal: indicates lower motor neuron pathology at the level of the peripheral nerve or root

--generalized: peripheral neuropathies--diabetic, alcoholic, inflammatory (Guillain-Barre). Myopathy may also cause hyporeflexia.

Hyperreflexia

--focal: indicative of upper motor neuron pathology; frequently associated with upgoing toes on testing of the Babinski's sign--this cannot be secondary to lumbar spine disease since there are no UMNs in the lumbar spine

--generalized: suggestive of increased arousal, hyperthyroidism, drug toxicity

Grading Deep Reflexes

Grade 0	0	Absent
Grade 1	+	Diminished but present
Grade 2	++	Normal
Grade 3	+++	Normal
Grade 4	++++	Hyperactive
Grade 5	+++++	Hyperactive with clonus

From DeGowin EL, DeGowin RL: Bedside Diagnostic Examination, 3rd edition, Macmillan Publishing, New York, 1976, p.791.

E. Diagnostic Testing [37]

**Diagnostic Tests
for Low Back Pain**

	Accuracy	Sensitivity	Specificity
	(% agree with study)	(range of estimates)	
Clinical exam	45-76	.80	.82
Radiography	31	—	—
Myelography	72-91	.61-.95	.16-.95
CT or MRI	70-100	.80-.95	.58-.95
Discography	30	.83	.53-.78
Electromyography	78	.56-.72	—

1. Radiographic

No matter which radiographic technique is used, the results must always be correlated with clinical findings. As the above table[2, 4, 11, 17, 18, 19, 21, 23, 24, 27, 35, 40] of diagnostic tests for low back **pain** demonstrates, radiographic tests are far from perfect and serve best to confirm a clinically suspected diagnosis.

Plain films--value is limited to demonstrating bony pathology, some soft tissue tumors can be seen

Myelograms--involve the injection of contrast into the intrathecal space. For most of the common spinal diagnostic problems, CT or MRI are superior and free of the risk of post-dural puncture headaches.

Computerized Tomography (CT)--more bony detail and superior to MRI for bone or joint disease of the spine, including foraminal bony stenosis

Magnetic Resonance Imaging (MRI)--superior soft tissue contrast and superior to CT or myelography for diagnosis of spinal disc disease or neural compression secondary to spinal stenosis. Also best for evaluating spinal alignment, infection, or tumor.

Bone scans--radionuclide bone imaging identifies osteoblastic activity and can help with the diagnosis of bone tumor or metastatic disease, osteomyelitis, fractures, joint disease, avascular necrosis, and Paget's disease.

2. Diagnostic blocks [3]

Nerve blocks with local anesthetics can help to distinguish focal from referred **pain**, **somatic** from sympathetically mediated **pain**, central from peripheral **pain**, and can help identify which peripheral nerves may be involved. This can help to guide treatment with further blocks or with other medical and surgical interventions.

3. Electromyography & Nerve Conduction Studies (EMG / NCS)

These studies can assist in identifying and localizing functional lesions of peripheral nerves, motor units and muscle lesions. Such tests of function can be followed over time and complement the anatomic radiology studies.

NCS generally reflect conduction in the larger, faster, myelinated nerves.

4. Somatosensory evoked potential testing (SSEP)

SSEPs are better than EMG / NCS tests for assessing upper motor neuron diseases such as MS, syringomyelia, or spinal cord ischemia. SSEP testing involves the senses of touch, position, and vibration, rather than **pain** or temperature.

5. Other Quantitative Sensory Testing (QST)

Pain syndromes may represent dysfunction more specific to the small A-delta and C fibers. Testing of small fiber function is possible with devices which test thermal or electrical thresholds to perception and **pain**. Such testing is less invasive and may also be useful to monitor hyperesthetic responses.

Fiber Type (Group)	Innervation/Function [5, 8, 29]	Myelin	Mean Diameter (_m)	Mean Conduction Velocity (m/sec)
A-alpha (II)	Primary motor & propioception	+++	15	100
A-beta (II)	Cutaneous touch & pressure (& motor fibers)	++	8	50
A-gamma	Muscle tone (spindle efferents)	++	6	30
A-delta (III)	Mechanoreceptors, nociceptors, and thermoreceptors	++	3	20
B	Sympathetic preganglionics	+	3	7
C (IV)	Nociceptors, mechanoreceptors, thermoreceptors, sympathetic postganglionic	-	1	1

F. Psychological Evaluation

As discussed earlier, the clinician should always assess the patient's psychological state, and the emotions surrounding the **pain** problem. It is particularly valuable to inquire regarding:

· Neurovegetative symptoms

· sleep disturbance

· appetite disturbance

· loss of energy

· loss of libido

· anhedonia

· impaired concentration

· suicidal ideation

· Impact of the **pain** on the patient's

· day-to-day activities

· work & finances

· personal relationships

· recreational pursuits

Factors suggesting the need for more formal psychological evaluation include:

· Evidence of mood or anxiety disorders

· Evidence of substance abuse

· Evidence of psychotic disorder

· Evidence of cognitive impairment

· Evidence of overwhelmed coping capacities or suicidal ideation

· Evidence of prominent secondary gain

· Problems with hostility, anger, or personality disorder

· Suspicion of malingering or factitious disorder (e.g. inconsistent findings)

· Prolonged and extensive course of treatment failures

· Need for high dose opioids for non-malignant **pain**

· Assessment of suitability for aggressive invasive treatments

G. Differential Diagnosis

After completing the data gathering process, it is time to consolidate the findings into a

differential diagnosis. During this process the clinician should consider:

· The meaning of inconsistent findings?

· Consider psychogenic or malingering diagnoses, but beware that the emotional turmoil which surrounds chronic **pain** may falsely suggest these diagnoses.

· Be cautious about reaching a psychogenic diagnosis simply because the **pain** symptoms cannot be understood physiologically. The clinical and basic sciences of **pain** are rapidly progressing--what is not understood today may be understood tomorrow.

· Be wary of obvious diagnoses or therapies that were missed by other clinicians. Check with prior physicians about their findings.

· Do the signs and symptoms indicate the nature of the **pain**?

· nociceptive--suggesting tissue injury or inflammation

· **neuropathic**--indicating central or peripheral dysfunction of the nervous system

· **pain** with mixed features --such as migraine or possibly myogenic or myofascial **pain**

H. SUMMARY

A careful assessment of the patient with **pain** should include efforts to categorize the **pain**, to determine its etiology, and to consider associated medical, social, emotional and psychological factors. If the clinician can answer the six questions listed at the start of this chapter, then the patient will be well on the way towards receiving appropriate and comprehensive treatment.

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